Studies towards an enantioselective synthesis of epibatidine

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Studies towards an enantioselective synthesis of epibatidine

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Abstract

Chapter one is a comprehensive review of the synthetic work towards the alkaloid epibatidine. Detailed are all the published syntheses of the natural product up to and including, February 2002. The chapter also includes brief sections on the history of epibatidine's isolation and its intriguing biological profile.

Chapter two describes the synthetic strategy planned for the enantioselective synthesis of epibatidine. This key step of which is an enantioselective desymmetrising Suzuki-Miyaura coupling. This chapter also includes the literature precedents for enantioselective palladium catalysed cross coupling.

Chapter three describes the synthetic work carried out. The first part describes the construction of the 2,3-dihalide azabicyclo[2.2.1]heptenes and other model substrates required for the key Suzuki-Miyaura coupling reaction. This includes a Diels-Alder addition to a protected pyrrole, cleavage of the activating sulphone group and a halogenation addition and elimination sequence. An alternative strategy involving the preparation of protected 3,4 diiodo pyrrole in a Diels-Alder addition with a symmetrical dienophile is also examined.

The second part reveals the preliminary efforts towards optimising the palladium coupling chemistry. Included in this is the preparation of pyridine boronic ester species required as coupling partners to provide the natural product and the preparation of novel mono-phosphine ligands from commercially available C_2-symmetric diphosphine ligands. An initial enantioselective study with a commercially obtained boronic acid is described.

Chapter four provides detailed experimental procedures.

Acknowledgements

Firstly I would like to thank Dr Michael Willis for putting up with me for the last four and a half years. (It can't have been an easy task but he seems to have come through the experience relatively unscathed and can appear quite normal and lucid at times...) His enthusiasm and optimism never waned and he was always on hand and willing to offer advice and new ideas for the project. (Though his photocopying skills leave a little to be desired!)

Thanks also to Alan Nadin and the rest of the group at Merck for all the help and interest they showed during my very profitable three month stay in Harlow.

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Thanks to all my housemates during my PhD for making the time such a laugh, in particular those that made up the original four; Dr Diego "Say "What?" again! I dare you..." Oriato, Italy's very own Samuel L. Jackson impersonator and Lycra fetishist. Dr Jean-Philippe "I'll be there in ten minutes" Cros, France's most prompt man. Dr (well, in about decade or so) Hadi "Mc" Madani, Iran's most northerly and only haggis eating and kilt wearing ambassador. And last but not least Dr Arach "Hey man! " Goldar, France's second most prompt man and world-class afro modeller.

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Thanks to the organic chemistry golfing (well... pitch and putt) society and all its members, Gian Sohal, Jean-Philippe, Christian, Matthew Clarke, Matthew Leese, Stephen Flower, Paul Mendonca, and Kamlesh Chauhan, it has been a *real* pleasure losing to you guys again and again... And last but not least Kerry Jenkins. (Sorry Kerry, I couldn't really put you in before that last comment now, could I?) It was an excellent way to spend sunny summer (and any other season for that matter!) otherwise lab-bound afternoons watching Kerry relax and unwind!

I want to thank Fiona Collins for letting me crash at her place on campus in the last few months! And for her lifts to campus once a fortnight in the "blue bus"! I think they were the only times I managed to make it in to the lab before 9am...

To all the remaining gang from home... (Seth, Jon, Tim, Ewan, Geoff, Matthew, Richard, Laura, Lucy and Amanda)... you can stop asking me when I finish now! And yes I know, it has been a bloody long time since school and I still haven't got a job yet! Cheers guys!

Thanks to anyone else whom I have forgotten! (and anyone who has managed to read this far through this ramble..) Sorry, but it is about 3:30am and I am shattered....

Finally and most importantly thanks must go to my Mum and Dad and sisters Olivia and Annie who have seen me through nearly eight years at Bath University, both financially and emotionally! Its finally over now, I know you sometimes didn't believe this would ever end!

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Abbreviations

Ac	acetate
AIBN	2,2'-azobis(2-methylpropionitrile)
aq.	aqueous
app.	apparent
Ar	aryl
BINAP	2,2-bis(diphenylphosphino) binaphthyl
BOC	*tert*-butyl carbonate
BOC_2O	di-*tert*-butyl dicarbonate
Bn	benzyl
Bu	butyl
br	broad
Bz	benzoyl
BzCl	benzoyl chloride
C_{ar}	aryl carbon
cat.	catalytic
C_{brid}	bridgehead carbon
CBzCl	benzyl chloroformate
CI	chemical ionisation
conc.	concentration
C_{vin}	vinyl carbon
d	doublet
dba	dibenzylidineneacetone
DBU	1,8-diazabicyclo[5.4.0]-7-undec-7-ene
DCE	1,1-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylamino pyridine
DME	1,2-dimethoxy ethane
DMF	*N,N*-dimethyl formamide
DMSO	dimethyl sulphoxide
DPPA	diphenyl phosphoryl azide
dppf	1,1'-bis-(diphenylphosphino)ferrocene
DUPHOS	1,2 bis(2,5-dimethylphospholano)benzene
ee	enantiomeric excess
EI	electron impact
eq	equivalent
Et	ethyl

ether	diethyl ether
Et_2O	diethyl ether
EtOAc	ethyl acetate
ex.	exchangeable
FAB	fast atom bombardment
g	gram
h	hour
HPLC	high pressure liquid chromatography
^{i}Pr	iso-propyl
IR	infra red
JOSIPHOS	[2-(diphenylphosphino)ferrocenyl]ethyl dicyclohexylphosphine
K-Selectride	potassium tri-*sec*-butylborohydride
KHMDS	potassium hexamethyldisilazane
L	ligand
L*	enantiopure ligand
LDA	lithium di*iso*propylamide
LiHMDS	lithium hexamethyldisilazane
L-Selectride	lithium tri-*sec*-butylborohydride
LTA	lead tetraacetate
m	multiplet
m	*meta*
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
mg	milligram (s)
min	minute (s)
mL	millilitre (s)
MOP	2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl
Mp	melting point
MS	molecular sieves
MsCl	methanesulfonyl chloride
n	*normal*
NBS	*N*-bromosuccinimde
NMP	*N*-methyl pyrrolidinone
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
Ph	phenyl
q	quartet
PCC	pyridinium chlorochromate
Pd/C	palladium on charcoal
PG	protecting group
PHANEPHOS	4,12-bis(diphenylphosphino)[2,2]paracyclophane
phephos	(1-benzyl-2-diphenylphosphanyl-ethyl)-dimethyl-amine

PHOX	phosphinoxazoline
ppt	precipitate
Pt/C	platinum on charcoal
py/pyr	pyridine
quat.	quaternary
QUINAP	1-diphenylphosphino-1-napthyl)isoquinoline
Rh/Al_2O_3	rhodium on alumina
rt	room temperature
t	triplet
TBDMS	^{t}butyldimethyl silyl
^{t}Bu	*tertiary*-butyl
TBAF	tributylammonium fluoride
TEA	triethylamine
Tf	trifluoromethane sulphonate
Tf_2O	trifluoromethanesulphonic anhydride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	tri*iso*propyl silyl
TLC	thin layer chromatography
TMS	trimethyl silyl
Tol	tolyl
Tol-BINAP	2,2′-bis(di-p-tolyl-phosphino)-1,1′-binapthyl
Ts or tosyl	4-methyl-benzenesulphonyl
TsCl	4-methyl-benzenesulphonyl chloride
TsOH	toluene-4-sulphonic acid
t_r	retention time

Stereochemical notation

Throughout this thesis the graphical representation of stereochemistry is in accord with the convention proposed by Maehr.[1] Thus solid and broken wedges are used to signify absolute configuration while the use of solid and broken lines are used to signify racemic materials.

Racemic Single enantiomer

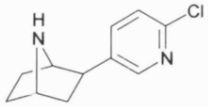
When wedges are used, narrowing of both solid and broken wedges indicate increasing distance from the viewer.

1 H.J. Maehr, *Journal of Chemical Education*, **1985**, 62, 114

Origin, properties and syntheses of epibatidine

Introduction

Epibatidine **1** is an alkaloid first isolated from the skin of an Ecuadorian poisonous frog by Daly and Myers in 1976 (Figure 1).[1]



1

Figure 1

It had in fact been discovered two years previously when extracts from frogs from two different populations, one in a cacao grove in the lowlands and the other from a road side seepage area in the highlands both contained a trace quantity of a compound that was shown to elicit a Straub tail reaction in mice;[2] a reaction that is typical of opioid alkaloids. The frogs from the two sites differed in size and colour but were found to be the highland and lowland extremes of the same species, *Epipedobates tricolor* (Figures 2[3] and 3[4]).

Figure 2

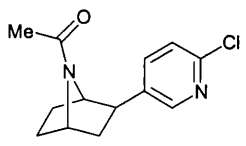
Figure 3

Because of the Straub-tail reaction a second field trip was planned to obtain the alkaloid in sufficient quantities for structural analysis. In the field trip undertaken in 1976 Daly and Myers discovered that in the two years since their last visit, the whole population of the lowland frogs in the cacao grove had inexplicably vanished. Identical appearing frogs were found on near-by banana plantations and a large collection was made. To their surprise, these frogs contained virtually no alkaloids at all. Fortunately for Daly and Myers, the highland site of the frogs was still highly populated and 750 skins were obtained which yielded on extraction less than 1 mg of the alkaloid.

All that could be determined at the time with the small quantity that was isolated was that the alkaloid possessed an empirical formula of $C_{11}H_{13}N_2Cl$, a secondary nitrogen that could be acylated and most likely contained a chloro-pyridine moiety. The limited power of NMR and MS techniques in 1980 was such that Daly and co-workers were unable to propose a structure with such a small amount of material.

A field trip carried out in 1982 to try and obtain more of the compound failed due to a change in the road system in the site in Ecuador that caused the loss of the remaining highland population of the frogs. Frogs from a nearby site were discovered to contain the alkaloid but unfortunately not in quantities sufficient for isolation. Further frustration was caused in 1984 when the Convention on International Trade in Endangered Species (CITES) placed the species *Epipedobates tricolor* (and all other dendrobatid frogs) on their Appendix II listing. This virtually ruled out any further field trips to obtain more of the compound because the numbers of frogs required for such trace compound extraction would prevent any permits or licences being granted. Effectively, Daly and co-workers now possessed the only remaining natural sample of the alkaloid available for study. Some of the meagre and precious sample had been used to demonstrate that the compound was 200 times more potent an analgesic than morphine. Its analgesic effect was also found, unlike morphine, not to be blocked by naloxone, an opiate antagonist; this result was strong evidence that the analgesic effect had a non-opiate mode of action.

It was not until 1990 that technical advances in NMR spectroscopy led Daly and co-workers to consider structural analysis by ^1H NMR spectroscopy alone. To gain the necessary degree of purity to carry out the NMR analysis, the alkaloid was first acetylated to enable removal of basic impurities *via* an acid extraction. Once purified the NMR analysis of the acetylated compound provided the structure 2 (Figure 4). The analysis was complicated due to the slow isomerisation of the *N*-acetyl rotamers, with both forms appearing in the spectra in a 1:1 ratio.



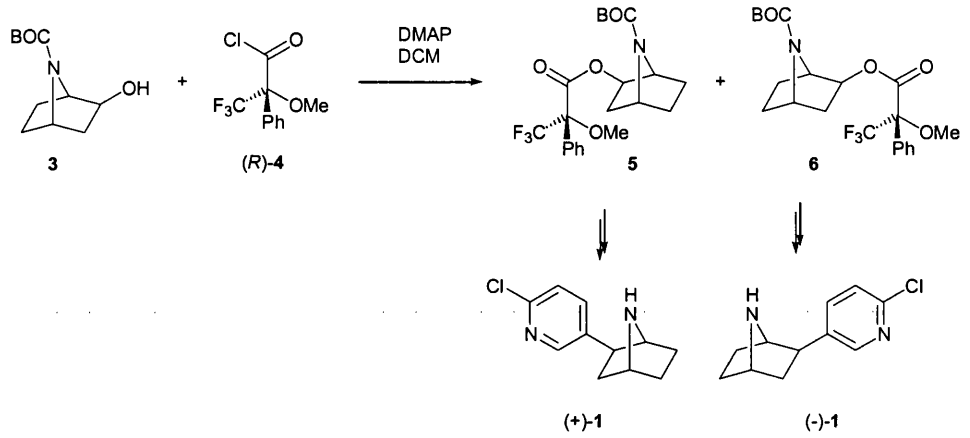
2

Figure 4

In 1992 the alkaloid was then named epibatidine and this result was then published along with the preliminary biological properties.[5] The publication sparked off synthetic efforts by different groups around the world to prepare and determine the absolute configuration of natural epibatidine.

Determination of absolute configuration

The absolute configuration of epibatidine was determined by Fletcher *et al.*[6] They separated the racemic alcohol **3** (a key substrate in their synthesis) *via* conversion to their Mosher's esters **5** and **6** that were then separable *via* crystallisation and flash chromatography (Scheme 1).

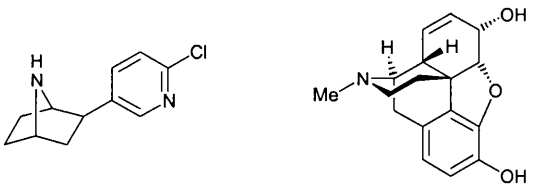


Scheme 1

The (-)-enantiomer proved to be the natural compound by comparison to the natural sample by HPLC analysis. Initially there was some confusion over this as it was first reported to be the (+)-enantiomer. This was due to the original optical rotation being measured as the oxalate salt, which has a positive rotation, whilst the free base has the negative rotation.[7]

Biological properties of epibatidine

The initial studies carried out by Daly and co-workers had shown that epibatidine caused the Straub tail reaction in mice.[2, 8] This reaction is characteristic of opiate alkaloids and has been used as an assay for opiate agonists and antagonists.[9] In comparison with the opiate morphine **7**, (Figure 5) which elicits a Straub tail reaction at 10mg/kg dosage, epibatidine achieved the same result with a 20μg /kg dose. The dosage of known opiate antagonist naloxone blocked the Straub tail reaction of morphine but only slightly reduced the effect induced by epibatidine, strongly suggested that epibatidine had a non-opiate mode of action. Binding studies also supported this theory; showing that epibatidine was 9000-fold less potent than morphine at the opioid receptors.



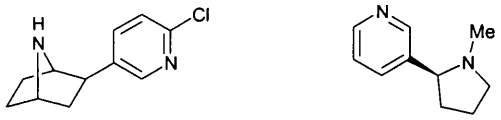
(-)-**1** **7**

morphine

Figure 5

Given this activity, and morphine's well-known analgesic properties, epibatidine was tested for analgesic induction using the hot plate assay.[10] (This consists of placing a mouse on a hotplate at an elevated temperature and measuring the time till the first signs of discomfort or agitation.) A striking result was also obtained in this assay. Epibatidine was found to have an ED_{50} of 5 μg/kg in the hotplate assay. Morphine, the standard, has an ED_{50} of 1 mg/kg. Thus epibatidine had shown a 200-fold increase in potency over morphine in this assay.

With the preparation of the first synthetic epibatidine, much more detailed biological studies could be carried out. The similarity between the structure of epibatidine and nicotine (-)-**8** (Figure 4) had been noted and it was perhaps not surprising that epibatidine was found to be active, exclusively, at the nicotine acetylcholin receptor.[7, 11]



(-)-**1** (-)-**8**

nicotine

Figure 6

Epibatidine was found to have 20-fold the potency of nicotine for the nicotinic receptors. Remarkably there was little difference between the enantiomers in their activity. The analgesic activity displayed by epibatidine is blocked by the nicotinic antagonist mecamylamine, but the initial analgesia results were confirmed. Epibatidine was 200 times more effective than morphine at inducing analgesia.

Unfortunately *in vivo* studies have highlighted the toxicity of the compound with doses as low as 40-86 μg/kg producing convulsions and death in mice.[12, 13]

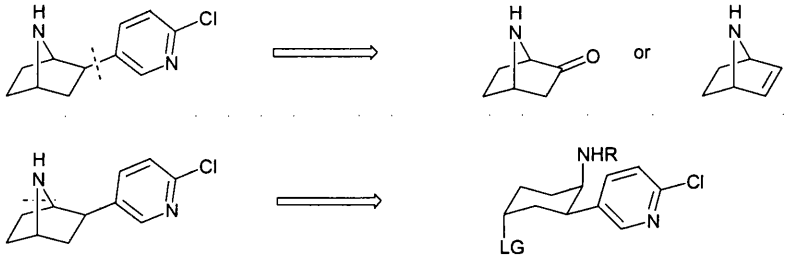
The result caused such widespread interest due to the therapeutic need for a potent analgesic to treat long-term chronic pain that would be free of the serious side effects inherent in morphine and related opiate drugs; such as sedation and the high risk of addiction and dependency.

Syntheses of epibatidine

The following section is intended to be a fully comprehensive review of the synthetic efforts towards epibatidine. All syntheses published, up to and including February 2002, are included.

Retrosynthesis of epibatidine

Retrosynthesis of the epibatidine molecule reveals the two main strategies that have been used for its synthesis (Scheme 2). The first potential disconnection is the carbon-carbon bond between the bicycle and the chloro-pyridine moiety and would produce ketone or alkene aza[2.2.1]bicycles. This strategy would require the formation of the bicycle in the early stages of the synthesis and end with the coupling to the aromatic portion. The second option would be to disconnect the bond between the nitrogen and bridgehead carbon. This would produce a substituted cyclohexane compound leading to the formation of the bicyclic structure of epibatidine at the very last stages of the synthesis.

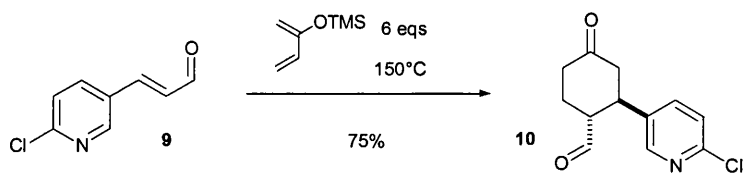


Scheme 2

The syntheses of epibatidine are divided according to the two main strategic plans. Three additional categories arise from the syntheses that derive from the chiral pool, enzymatic approaches to the synthesis and miscellaneous syntheses.

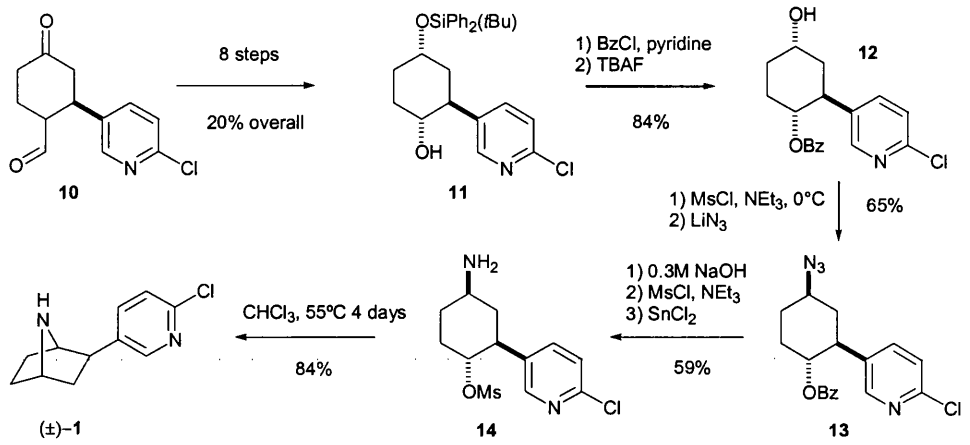
1) Synthesis via ring closure of a substituted cyclohexane derivative

The first synthesis of epibatidine that appeared in the literature was that of Broka in 1993.[14] Broka utilised a Diels-Alder reaction between the enal **9** (prepared in one step from 6-chloropyridine-3-carboxaldehyde **24**, Scheme 6) and 2-(trimethylsilyloxy)-1,3-butadiene to form the basic cyclohexane ring structure of keto-aldehyde **10** (Scheme 3).



Scheme 3

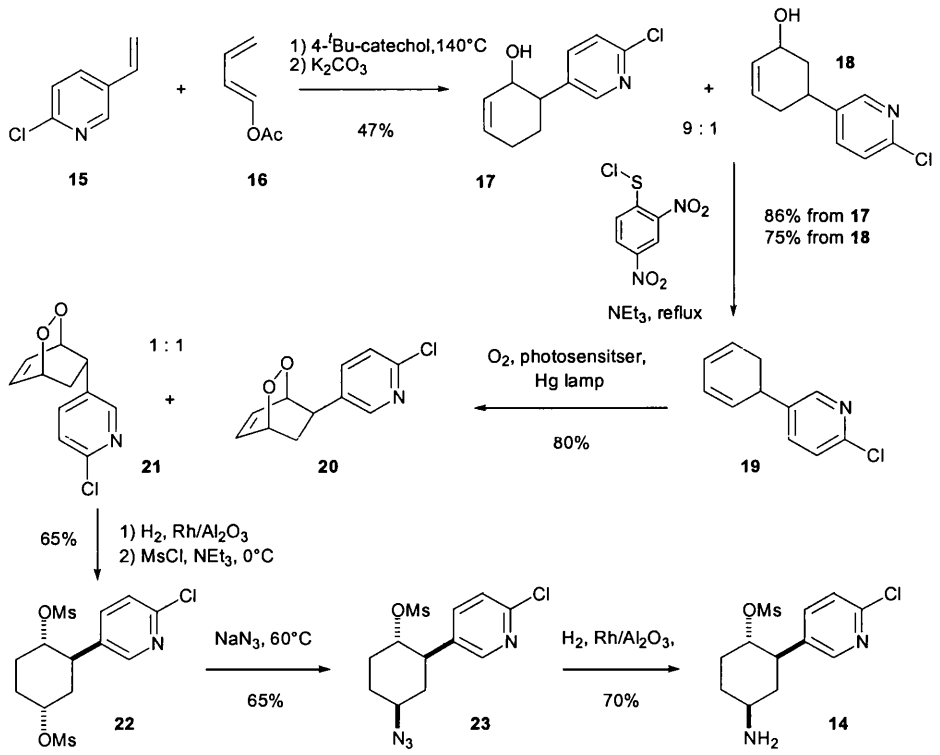
Unfortunately aldehyde **10** contained an additional carbon atom that has to be removed and this requires considerable manipulation of the molecule. No less than eight reactions were required to transform aldehyde **10** to the TBDPS protected *cis*-diol **11** (Scheme 4). The free hydroxyl was converted to its benzoate and treatment with TBAF then freed the silyl protected hydroxyl group, which gave alcohol **12**. The free hydroxyl was activated *via* mesylate formation followed by S_N2 substitution by lithium azide to form azide **13**. This generated the desired stereochemistry on the cyclohexane ring for ring closure. All that remained was the reduction of the azide to the amine and conversion of the benzoate to the mesylate to yield epibatidine precursor **14**. The ring closure occurred in a respectable 84% yield after heating for four days in chloroform.



Scheme 4

This synthesis was far from ideal. In particular the sequence of steps to generate alcohol **11** makes the route time consuming and cumbersome. The synthesis however, did demonstrate the efficacy of the substituted cyclohexane ring closure strategy to form the aza[2.2.1]bicycloheptane structure.

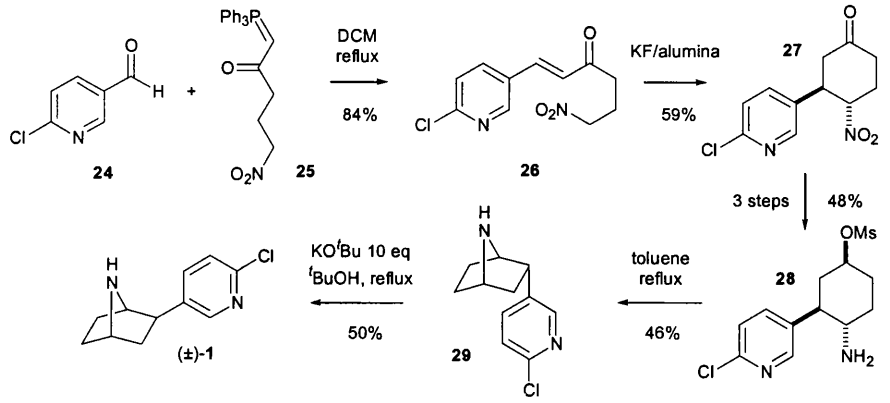
With the successful ring closure of mesylate **14** to epibatidine demonstrated by Broka, an efficient synthesis of mesylate **14** (and its isomers and equivalents) then became the target of other groups attempting the total synthesis of epibatidine. Ko and co-workers, in 1994, utilised a reaction of singlet oxygen with cyclohexadiene **19** as the key step in their approach (Scheme 5).[15] Their synthesis also used a Diels-Alder reaction to generate the required cyclohexane. Vinyl pyridine **15** was heated with 1 acetoxy-1,3-butadiene and the resultant cyclisation adducts were hydrolysed to yield a 9:1 mixture of regio isomeric allylic alcohols **17** and **18**. Both of the alcohols were converted *via* dehydration to the single cyclohexadiene product **19** in high yield. The reaction of the diene with oxygen under photochemical conditions gave a 1:1 mixture of *endo* **21** and *exo* **20** arylated products. The *endo* isomer **21** was reduced and the resultant diol was converted to the *bis* mesylate **22**. Treatment with one equivalent of NaN_3 yields only azide **23** and a small amount of the *bis* azide. Reduction of azide **23** furnishes the epibatidine precursor, mesylate **14** in a 70% yield. The mesylate **14** was converted to epibatidine in 78% yield under the Broka conditions.



Scheme 5

This synthesis was limited only by the lack of control of the addition of singlet oxygen to the diene **19**. The alternate *exo*-adduct may possibly have been converted to epibatidine *via* an epimerisation strategy though the authors did not investigate this.

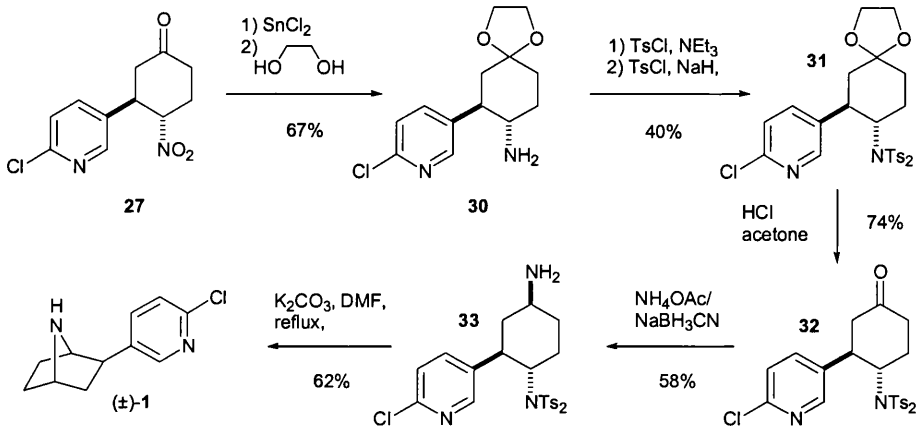
Another route to the mesylate, though this time a *trans* isomer **28**, was disclosed by Szantay *et al.* in the same year (Scheme 6).[16] Wittig reaction of aldehyde **24** and phosphorus-ylide **25** gave alkene **26** in high yield. Treatment of **26** with KF/alumina induced cyclisation to cyclohexane **27** in 59% yield. Reduction of the ketone with $NaBH_4$ was stereoselective and was followed by mesylation of the resultant alcohol and reduction of the nitro group with $SnCl_2$ to yield amine **28**. Ring closure was carried out in toluene at reflux and produced the *endo* isomer of epibatidine in low yield, which was then epimerised to the natural product in 50% yield by treatment with KO^{t}Bu in ^{t}BuOH at reflux.



Scheme 6

This synthesis is short with no protection or deprotection steps but is hampered by the low yielding S_N2 displacement of the *trans* mesylate **28**. This result was curious with the knowledge that its isomers **14** and **41** undergo the same reaction in chloroform much more efficiently and cleanly (Schemes 4, 9 and 11). The epimerisation step was also undesirable due to its inefficiency in forming the natural *exo* stereochemistry of the chloro-pyridine moiety. However the success of this strategy then enabled *endo* isomer **29** to become a viable intermediate for later synthetic attempts.

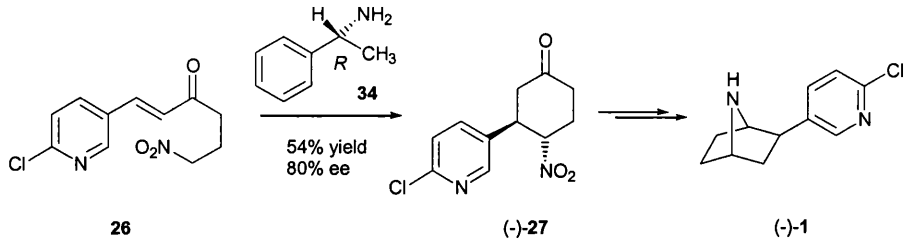
Aware of the shortcomings of their first synthesis, Szantay *et al.* disclosed a modified version in 1996 to avoid the low yielding ring closure and epimerisation steps (Scheme 7).[17] Nitro **27** was instead reduced to the amine and the ketone protected as its cyclic acetal **30**. *Bis* tosylation of the free amine occurred in two steps and removal of the acetal-protecting group under acid conditions gave ketone **32**. Selective reductive amination then provided amine **33** in 58% yield. Ring closure to form epibatidine was then carried out with K_2CO_3 in DMF at reflux in moderate yield. Unfortunately for Szantay *et al.* the modifications employed in Scheme 7 failed to bring about any improvement in overall yield.



Scheme 7

In their efforts to produce an enantioselective version of their synthesis, the first to be published, Szantay *et al.* looked at replacing KF with chiral amines in the ring closure of nitro **26** to cyclohexanone **27** (Scheme 6).[17] Only primary amines affected this transformation and the highest enantioselectivity was obtained

using α-phenyl ethylamine **34** (Scheme 8). The reaction of nitro **26** with (*R*)-**34** produced cyclohexane (-)-**27** in a 54% yield and 80% ee. Cyclohexane (-)-**27** was converted into the natural enantiomer of epibatidine using the steps outlined in Schemes 7 or 8.



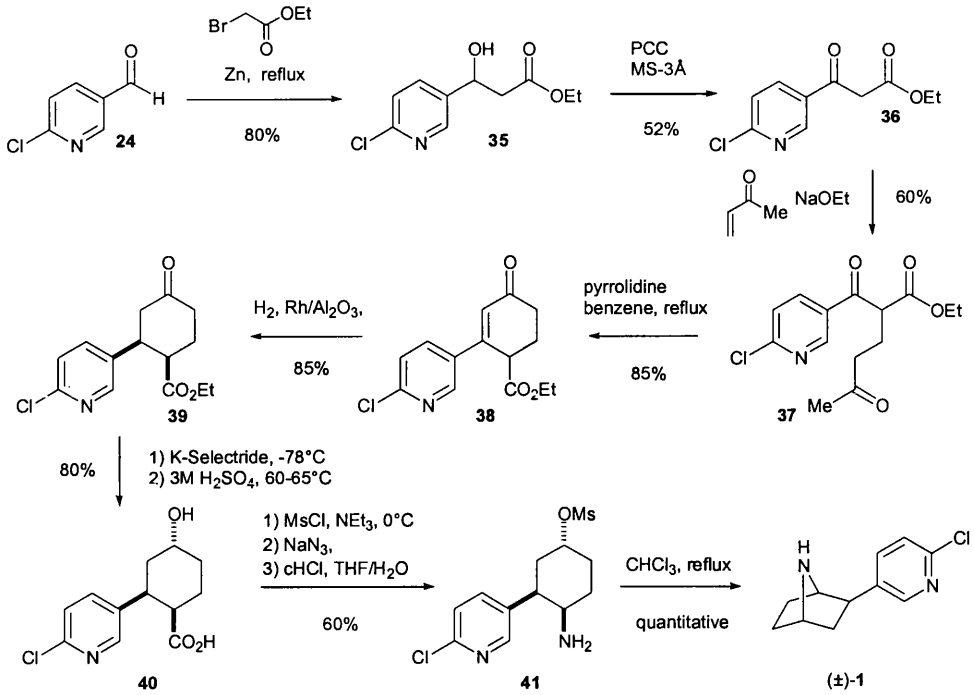
26 (-)-**27** (-)-**1**

Scheme 8

This was a successful and efficient adaptation of their earlier studies to provide the first enantioselective synthesis of epibatidine. Both enantiomers of the product could be obtained from the enone **26** with the use of the (*R*)- or (*S*)- enantiomers of amine **34**. The cyclised products, **27** were obtained in enantiopure form after a single recrystallisation.

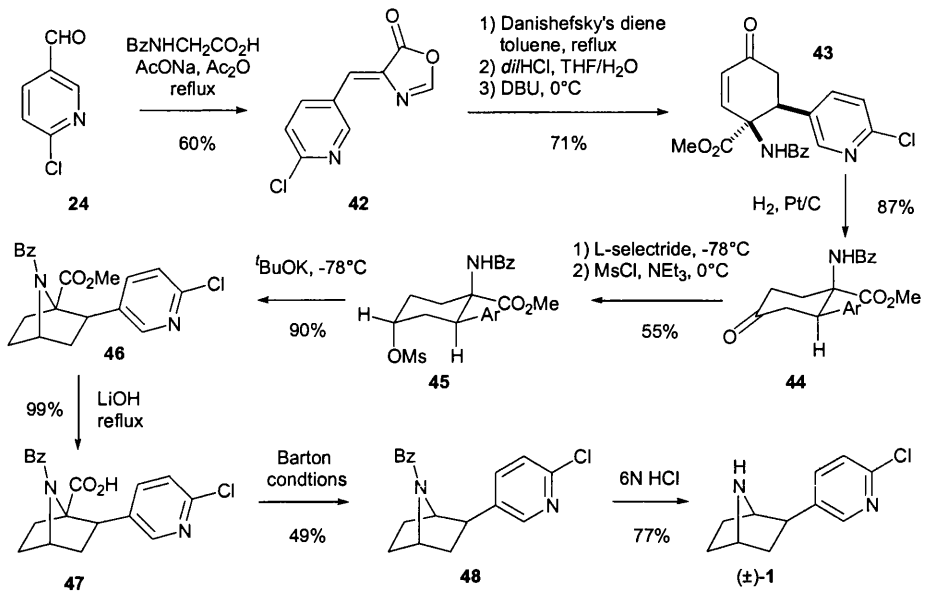
A much more recent synthesis by Kitahara and co-workers, in 2001, approached the synthesis of the mesylate **41** *via* a Robinson annulation between β-keto ester **36** (prepared in two steps from 6-chloropyridine-3-carboxaldehyde **24**) with methyl vinyl ketone (Scheme 9).[18] The diketone **37** underwent an intramolecular aldol addition and cleanly formed the cyclised ester **38**. Reduction of the enone was performed with H_2 and Rh/Al_2O_3 and yielded the desired ketone **39** as the major product. Selective reduction of the ketone was carried out with K-selectride and the ester moiety was hydrolysed in 3M H_2SO_4. Activation of the hydroxyl, displacement with NaN_3 and subsequent Curtius/Hoffmann type rearrangement afforded amino-mesylate **41** in a 60% overall yield. Conversion to racemic epibatidine was quantitative from amine **41** in $CHCl_3$ at reflux.

This reaction sequence demonstrated improved conditions for the ring closure of a substituted mesylate (**41**) to form epibatidine.



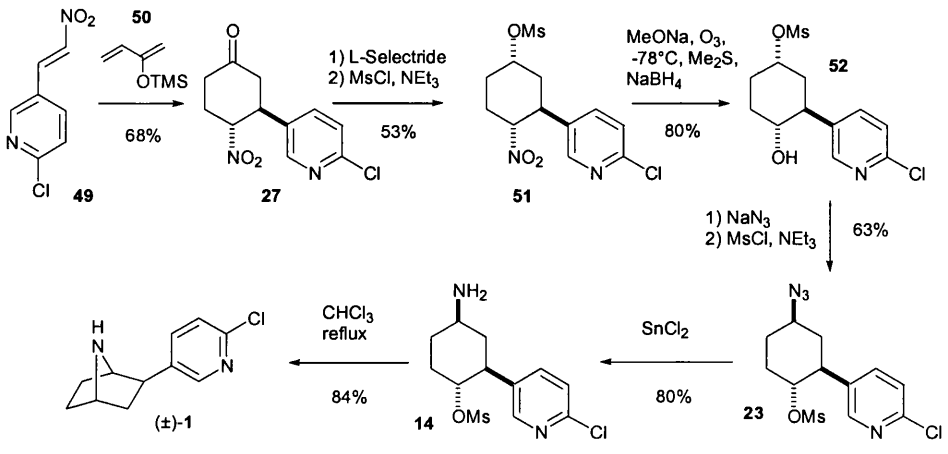
Scheme 9

Avenoza and co-workers also utilised a Diels-Alder reaction to form their azabicyclo[2.2.1]heptane precursor **45** (Scheme 10).[19] Dienophile **42** (prepared in one step from 6-chloropyridine-3-carboxaldehyde **24**) was reacted with Danishefsky's diene in toluene at reflux. The two cycloadducts were hydrolysed in acid and treated with DBU to give solely enone **43** in a 71% yield. After reduction of the double bond, the ketone was treated with L-selectride to give a 7:3 mixture of equatorial and axial alcohols. The two isomers were separated by flash chromatography only when converted to their corresponding mesylates. The desired axial mesylate **45** was obtained in a 55% yield from ketone **44**. Bicycle **46** was obtained in an excellent yield from the mesylate **45** under basic conditions at -78°C in THF. Removal of the superfluous ester moiety was achieved by sequential hydrolysis to the acid **47** and then radical decarboxylation *via* the Barton ester. Deprotection of the benzoylated amine **48** to give epibatidine was achieved in HCl at reflux. This synthesis offered a rapid entry into the core structure of epibatidine. The only real weaknesses are the moderate yield of the desired mesylate **45** from ketone **44** and the low yield for the decarboxylation of acid **47**.



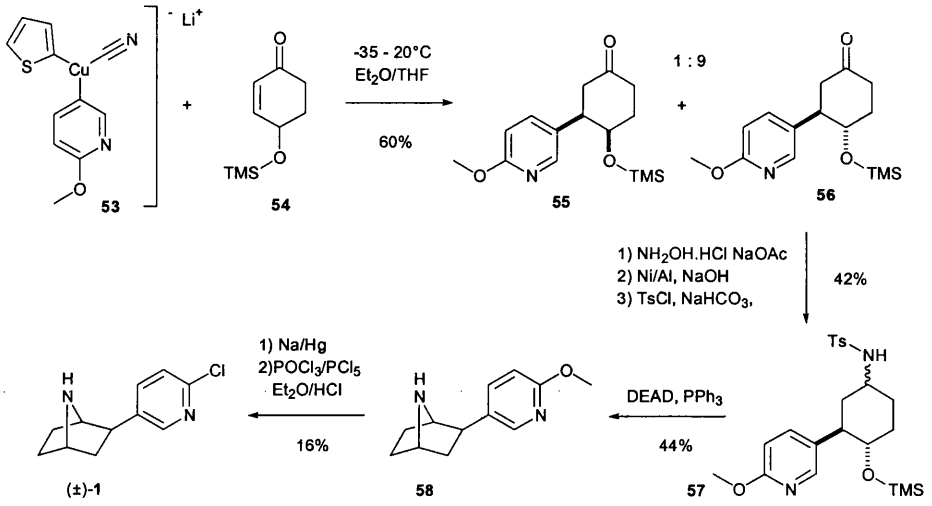
Scheme 10

Albertini and co-workers also made use of a Diels-Alder reaction during their construction of amino cyclohexane **14**, (Scheme 11).[20] Nitro dienophile **49** (prepared from 6-chloropyridine-3-carboxaldehyde) reacts with silyloxy diene **50** to form nitro-substituted cyclohexane **27** that was also an intermediate in the Szantay group's synthesis (Scheme 6 and 7). In order to avoid the low yielding epimerisation step in their synthesis, Albertini *et al.* looked to generate the desired *cis* relationship of amine and pyridine groups in **14**. Reduction of ketone **27** with L-selectride gave a 7:3 inseparable mixture of alcohols with the desired *anti* chemistry being favoured. The alcohols were separable as their mesylate derivatives. The desired isomer **51** was converted to the alcohol **52** *via* Nef conditions followed by *in situ* reduction of the carbonyl with $NaBH_4$. This transformation was achieved with complete retention of the stereochemistry. The mesylate was then displaced with sodium azide and the free hydroxyl was in turn converted to its mesylate to provide azide **23**. Reduction of the azide with $SnCl_2$ and subsequent cyclisation furnished racemic epibatidine in 67% yield.



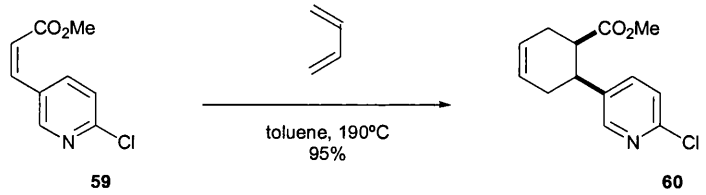
Scheme 11

Sestanj and co-workers approached the synthesis of bicycle precursor **57** using a 1,4 conjugate addition strategy (Scheme 12).[21] Enone **54** was treated with the higher order cuprate **53** to give a 9:1 mixture of ketones **56** and **55**. The ketone **57** was then converted to its oxime, which was reduced and tosylated to give cyclisation precursor **57** as a mixture of stereoisomers in an overall 42% yield. Intramolecular Mitsunobu reaction then provided bicycle **58** in a 44% yield. Deprotection of the tosyl group was carried out with sodium amalgam and transformation of methoxy group was achieved with PCl_5 and $POCl_3$ in two 40% yielding steps (16% overall) to yield (±)-epibatidine. The synthesis was relatively concise but the overall yield was low due to several inefficient steps.



Scheme 12

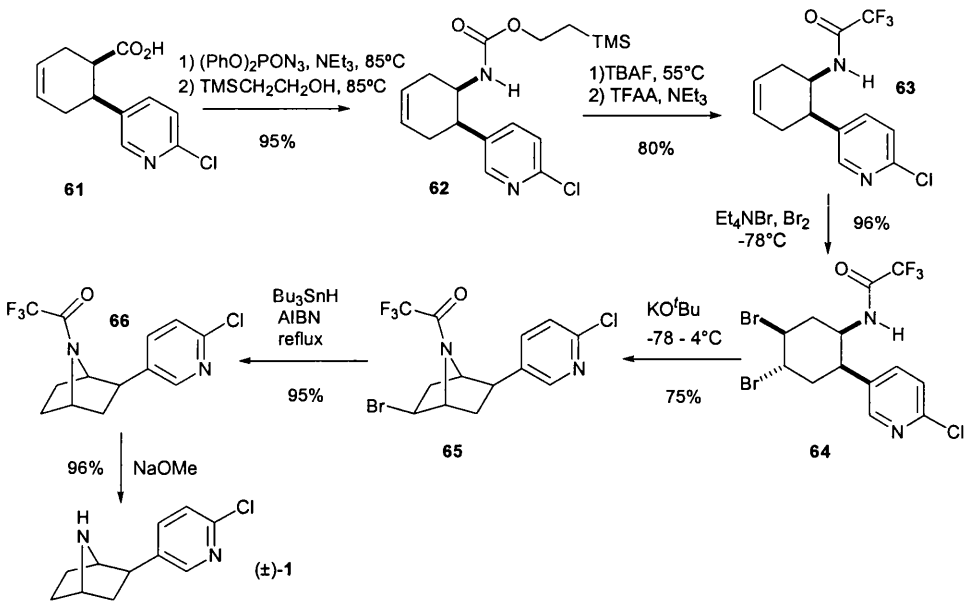
In 1993, a Diels-Alder strategy was employed by Corey and co-workers in their racemic synthesis of epibatidine.[22] Ester **59** (which was also prepared from 6-chloropyridine-3-carboxaldehyde **24** (Scheme 13) in one step) was reacted with butadiene to form the *cis* substituted cyclohexane structure **60** as a single adduct cleanly and in excellent yield (Scheme 13).



Scheme 13

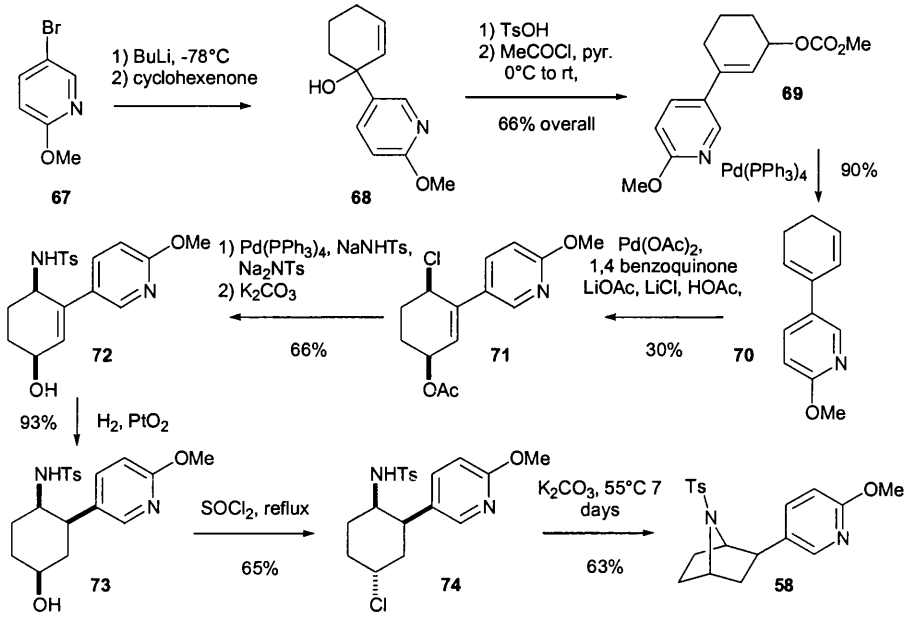
The nitrogen atom needed for the aza-bicycle was introduced to replace the extraneous methyl ester in an efficient process after quantitative saponification of ester **60** (Scheme 14). The acid **61** was then converted into an acyl azide that underwent a Curtius rearrangement in the presence of 2-TMS-ethanol to yield the carbamate **62** in good yield. The carbamate was cleaved and the nitrogen was acylated with trifluoroacetic anhydride to give trifluoroacetamide **63**. This compound was brominated to form dibromide **64** cleanly and stereospecifically in the presence of bromine ion. The bicycle was then formed *via* a base promoted

internal nucleophilic displacement to form bromide **65**. The additional bromine was removed under radical conditions with AIBN and $HSnBu_3$ and subsequently the trifluoroacetate group was cleaved with NaOMe in methanol to give (±)-epibatidine in excellent yield.



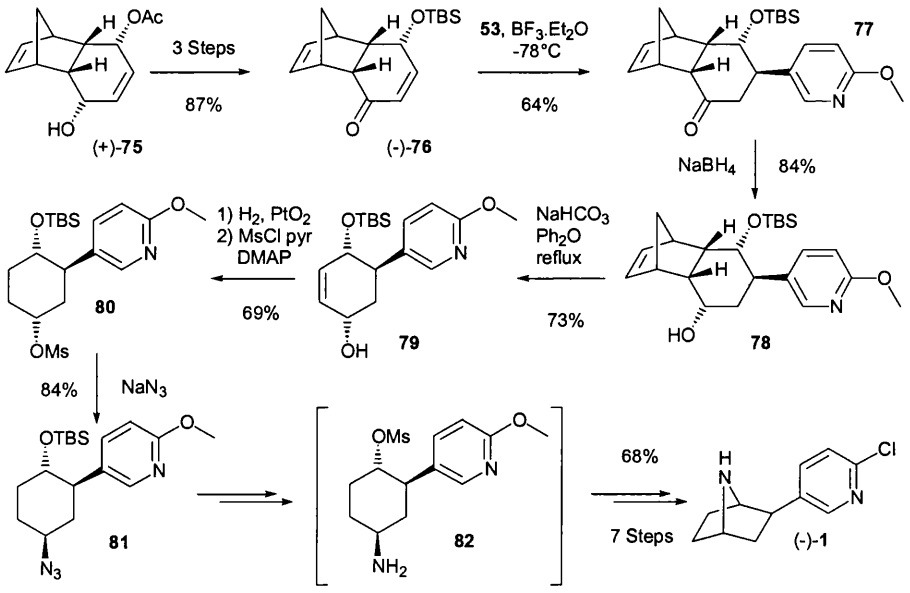
Scheme 14

Backvall and co-workers used a 1,4 oxidation strategy of 2-pyridyl-1,3-cyclohexadiene **70** in their synthesis of epibatidine (Scheme 15).[23] This was prepared from 5-bromo-2-methoxy pyridine **67**, which was lithiated and reacted with cyclohexenone to give the 1,2 addition product **68**. Treatment of the addition product **68** with acid gave a rearranged allylic alcohol that was reacted with methyl chloroformate to give carbonate **69** in an impressive 66% yield from bromo-pyridine **67**. Regioselective elimination was carried out by $Pd(PPh_3)_4$ in THF to form the diene **70** in high yield. Palladium (II) catalysed chloro-acetoxylation gave *cis* acetoxy-chloride **71** in a regio and stereoselective, if low yielding reaction. Stereospecific allylic substitution gave the *cis* amide and hydrolysis of the acetate gave allylic alcohol **72** in 66% yield. Hydrogenation proceeded smoothly to form a single diastereomer, alcohol **73**. The hydroxyl was then converted to the chloride with inversion of stereochemistry to give the required *trans* cyclisation precursor, chloride **74**. Cyclised adduct **58** was isolated in 63% yield after 7 days in MeOH at 55°C. Bicycle **58** was a known epibatidine precursor when this work was published and to complete the synthesis the chemistry developed by either Sestanj (Scheme 12) or Natsume (Scheme 43) can be applied.



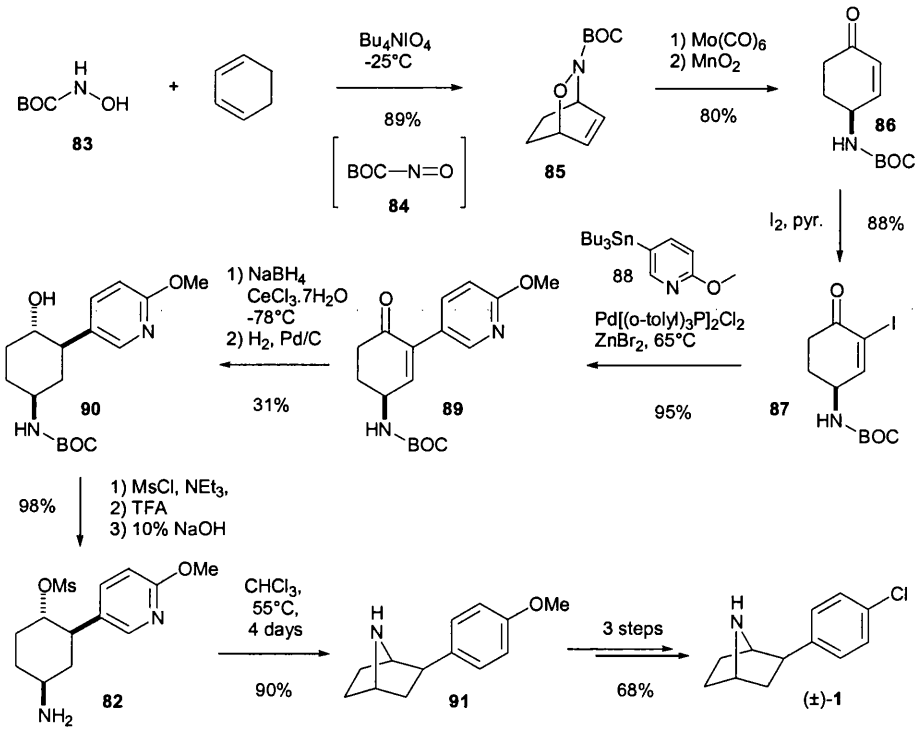
Scheme 15

A stereocontrolled route to (-)-epibatidine *via* the Broka mesylate isomer intermediate **82,** from a chiral *cis* alcohol (+)-75 was published by Ogasawara and co-workers in 1999 (Scheme 16).[24] This mono-protected diol was converted in three steps to the enone **76** in excellent yield. A higher order cuprate **53** (shown in Scheme 12), was used in a 1,4 conjugate addition reaction, to prepare adduct **77** as a single stereoisomer. Selective reduction from the convex face with $NaBH_4$, gave alcohol **78**. Retro Diels-Alder reaction, extruding cyclopentadiene provided cyclohexene **79** in good yield. Hydrogenation of the double bond, followed by mesylation of the hydroxyl yielded mesylate **80** in a 69% yield. Nucleophilic displacement of the mesylate with sodium azide gave azide **81**, which was converted to the natural enantiomer of epibatidine by chemistry previously published by Johnson (Scheme 17).



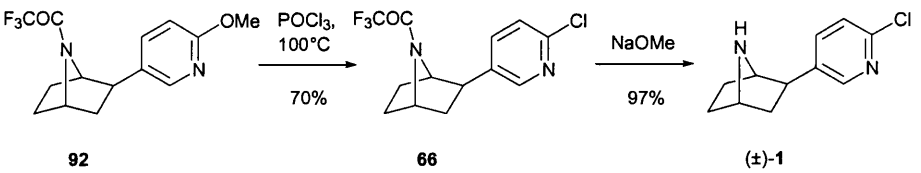
Scheme 16

Johnson and co-workers utilised a hetero Diels-Alder reaction between the nitroso species **84** (generated from **83** *in situ*) and cyclohexadiene in their route through to mesylate **82** (Scheme 17).[25] This generated the carbamate adduct **85** in high yield. Reductive cleavage of the *N-O* bond and oxidation of the resulting allylic alcohol gave enone **86**. The α-iodinated enone **87** was cleanly obtained by treatment of enone **86** with iodine in pyridine. A Stille coupling reaction between iodide **87** and methoxypyridyl stannane **88** was then performed to provide the aryl enone **89** in an excellent 95% yield. (The methoxy-substituted pyridine was used due to the sensitivity of the desired chloro substituent to reduction under hydrogenation conditions later in the synthesis.) Unfortunately the reduction of the ketone **89** led to a 2:1 mixture of diastereomers, the minor one being the desired *trans* alcohol **90**. Ring closure of the mesylated and deprotected amine **82** was achieved in warm chloroform over 4 days to give bicycle **91** in an excellent 90% yield.



Scheme 17

Conversion to epibatidine required the installation of the chloro substituent on the pyridine ring. This was achieved in three steps (Scheme 18). First the amine **91** was protected quantitatively as its trifluoroacetamide derivative **92**. This was then treated with $POCl_3$ under Vilsmeier conditions to give chloropyridine **66**. Lastly cleavage of the trifluoroacetamide group was achieved under basic conditions to yield epibatidine in excellent yield.

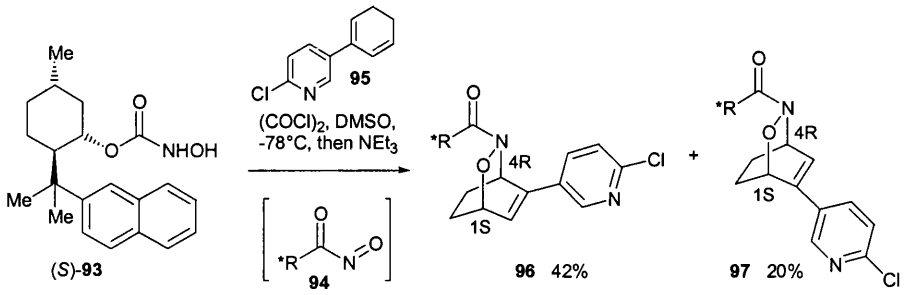


Scheme 18

The synthesis was highly successful aside from the lack of control of the reduction of enone **89**, which provided the desired alcohol **90** only as the minor product

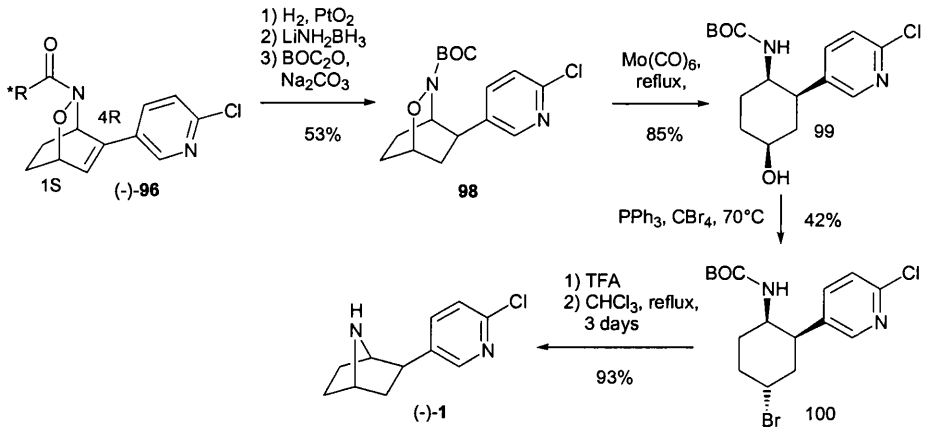
.

In 1998 Kibayashi and co-workers disclosed an asymmetric synthesis, utilising a chiral nitroso species as a dienophile in a Diels-Alder cyclisation (Scheme 19).[26, 27] Enantiopure hydroxamic acid **93** (prepared from (*S*)-pulegone in three steps and 79% overall yield) was oxidised under Swern conditions to the dienophile nitroso species **94**. This was reacted *in situ* with the pyridyl cyclohexadiene **95** to give cycloadducts **96** and **97** in respectively 42% and 20% yield.



Scheme 19

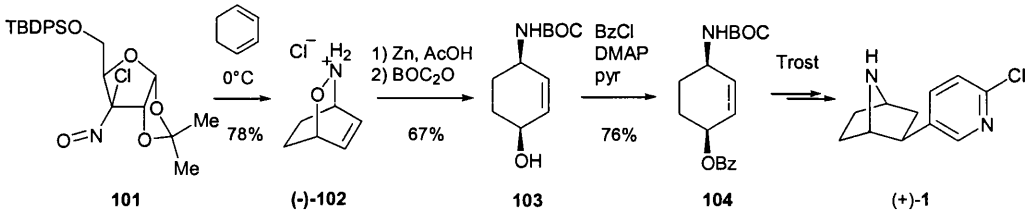
The isomer **96** was converted to (-)-epibatidine in the steps outlined in Scheme 20. Hydrogenation gave exclusively the *exo* isomer, which was followed by cleavage of the menthol auxiliary and protection of the nitrogen with BOC_2O to provide carbamate **98** in 53% yield. Reductive cleavage of the *N-O* bond was carried out with molybdenum hexacarbonyl to give the all *cis* substituted cyclohexane **99**. The hydroxyl was converted with inversion of stereochemistry to provide the cyclisation precursor, bromide **100** in 42% yield. Deprotection and cyclisation to (-)-epibatidine can be achieved in 93% yield from bromide **100**.



Scheme 20

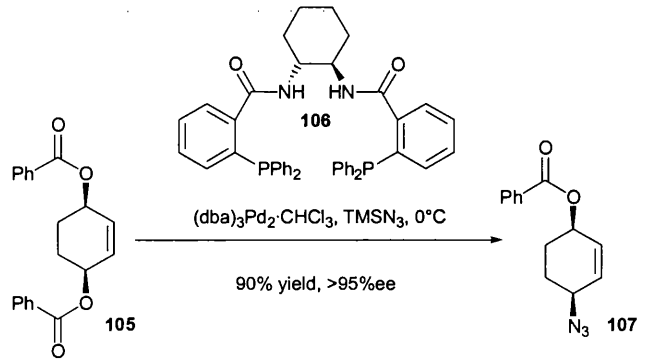
In 1999 Wightman and co-workers published an enantioselective synthesis of the unnatural enantiomer of epibatidine that also used an enantioselective nitroso Diels–Alder reaction as its key step (Scheme 21).[28] Chiral α-chloro nitroso **101** (derived from di-*O*-isopropylidene-α-D-glucofuranose) was reacted with 1,3 cyclohexadiene to provide enantiopure cycloadduct (-)-**102**. Reductive ring opening of the *N-O* bond with

zinc in acetic acid followed by protection of the amine gave enantiopure *cis* cyclohexene **103** in an overall 67% yield. Protection of the hydroxyl as its benzoate derivative gave *cis* cyclohexene **104**. This benzoate is enantiomeric with an intermediate Trost and Cook used in the second enantioselective synthesis of natural epibatidine and can therefore be converted using their synthetic route to the unnatural enantiomer of epibatidine (Schemes 22 and 23).



Scheme 21

Trost and Cook disclosed the second enantioselective synthesis of epibatidine in 1996.[29] The key step in their synthesis was the desymmetrisation of *meso* dibenzoate **105**, *via* a palladium catalysed allylic substitution. This was achieved using cyclohexane diamine ligand **106** with TMS-azide, to give enantiomerically pure **107** in a 90% yield (Scheme 22).



Scheme 22

The enantiomer of azide **107** can be obtained in high yield and same degree of enantiomeric purity using ligand **108** (Figure 7) under the same reaction conditions in place of ligand **106**.

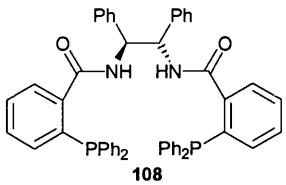
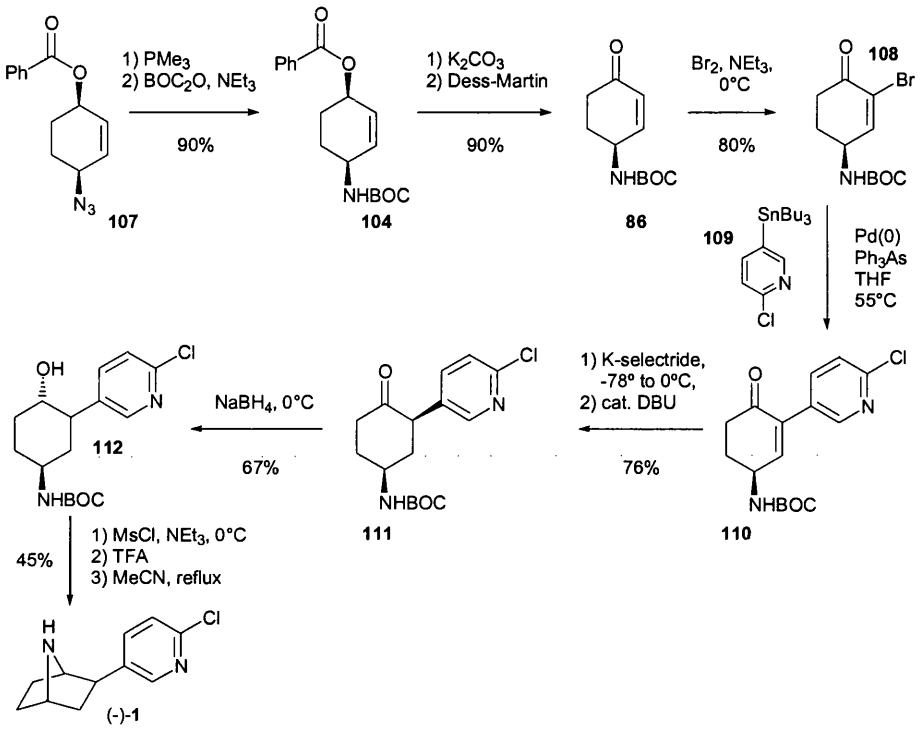


Figure 7

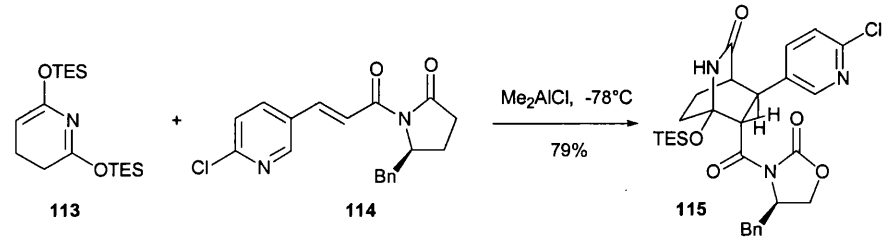
Azide **107** was converted to (-)-epibatidine *via* the steps outlined in Scheme 23. Reduction of the azide and subsequent protection of the amine with a BOC group was achieved in 90% yield. The benzoate **104** was hydrolysed and the resulting alcohol oxidised to form enone **86**, utilising the Dess-Martin periodane, in excellent yield. Selective α-bromination was achieved with bromine in the presence of triethylamine to

provide vinyl bromide **108**. The bromide was coupled successfully using Stille conditions with pyridyl stannane **109** to yield the arylated enone **110**. Reduction of the carbonyl with K-selectride gives a mixture of 4:1, *cis:trans* isomers that were equilibrated to the single *cis*-diastereomer **111** by treatment with DBU. $NaBH_4$ reduction of ketone **111** gave a 2:1 mixture of separable alcohol diastereomers in almost quantitative yield. The desired *trans* isomer **112** was the major product formed. The last three steps to furnish (-)-epibatidine; mesylation, deprotection of BOC group and cyclisation, were achieved in an overall 45% yield. These three steps were claimed to be un-optimised through time constraints.



Scheme 23

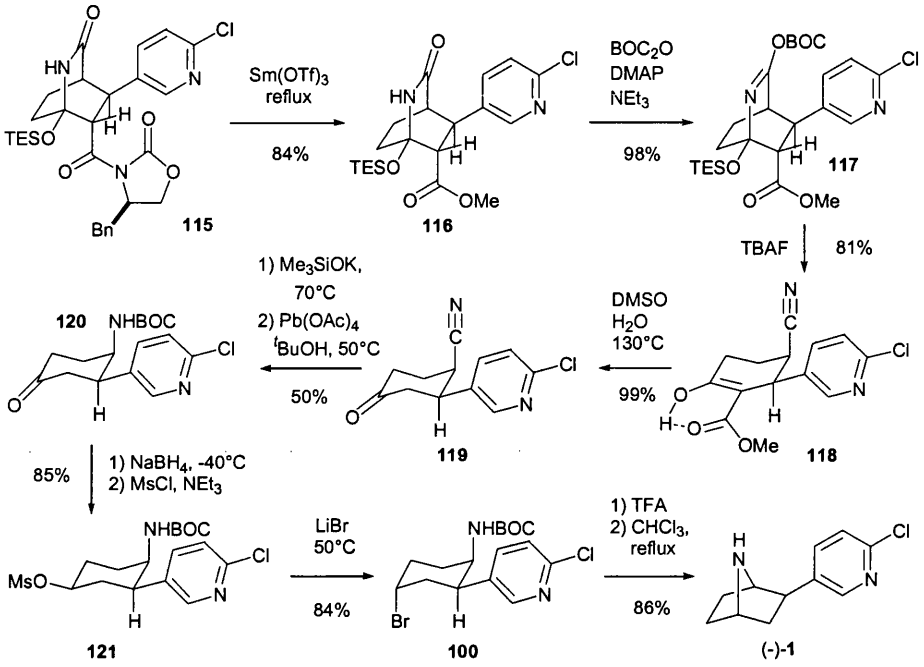
Evans and co-workers recently reported an enantioselective synthesis using an auxiliary controlled hetero Diels-Alder reaction (Scheme 24).[30] Diene **113** (prepared in one step from glutarimide) was treated with dienophile **114** (prepared using Horner-Wadsworth-Emmons reaction with 6-chloropyridine-3-carboxaldehyde **24**) at -78°C and Me_2AlCl to form bicyclic adduct **115**, as the *exo*-isomer with 90% de. The desired isomer was separated in a pure form, in a 79% yield from the product mixture.



Scheme 24

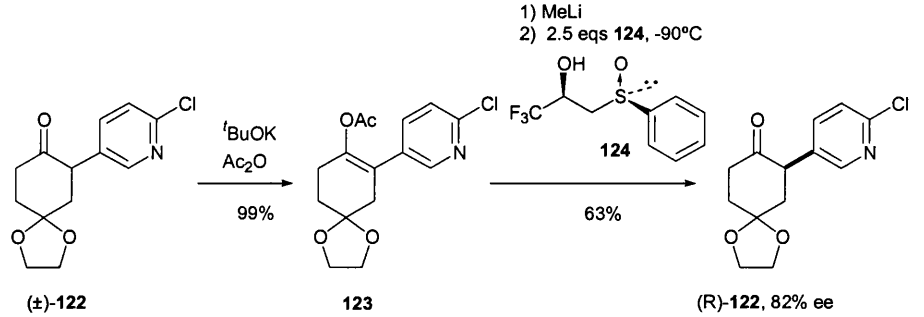
Cleavage of the auxiliary was achieved with $Sm(OTf)_3$ to yield lactam **116**, which was selectively *O*-acylated by treatment with BOC_2O and DMAP to yield carbonate **117** (Scheme 25). Reaction with TBAF

caused ring opening to form nitrile **118**, which was isolated exclusively as its enol tautomer. Decarboxylation of enol **118** under Krapcho conditions gave ketone **119** in nearly quantitative yield. Conversion of the nitrile to primary amide with Me_3SiOK followed by Hoffmann rearrangement induced with $Pb(OAc)_4$ and subsequent BOC protection yielded carbamate **120**. Reduction of the carbonyl with $NaBH_4$, gave a 92:8 mixture of equatorial:axial alcohols, which were separated as their mesylates. Equatorial mesylate **121** was then treated with LiBr under S_N2 conditions to give axial bromide **100** in an 84% yield. Deprotection and ring closure in $CHCl_3$ at reflux afforded (-)-epibatidine in 86% yield.



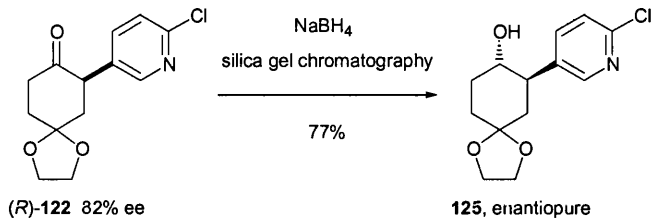
Scheme 25

An enantioselective synthesis of epibatidine has also been disclosed utilising an asymmetric protonation of a lithium enolate with a chiral β-hydroxy sulphoxide **124** (Scheme 26).[31] Kosugi *et al.* prepared racemic ketone **122** *via* the chemistry reported by Sestanj (with acetalisation of ketones **55** and **56** followed by deprotection of TMS group and Swern oxidation) in Scheme 12. Ketone **122** was converted into enol acetate **123** in nearly quantitative yield on treatment with KO^tBu and acetic anhydride. The lithium enolate formed by the reaction of **123** with methyl lithium was quenched with chiral sulphoxide **124** at -90°C to yield 63% of enantio-enriched, (*R*)-**122**, 82%ee.



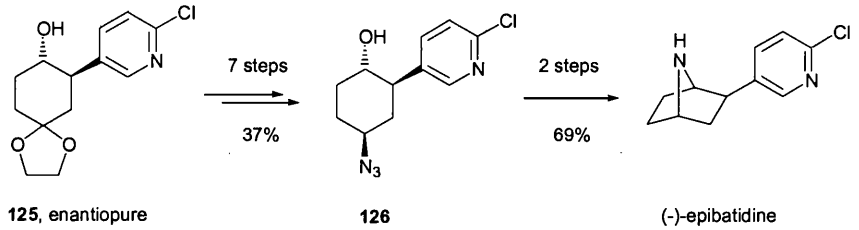
Scheme 26

The enantioenriched ketone (*R*)-**122** was reduced to alcohol **125** in 77% yield (Scheme 27). It was found fortuitously, that using achiral silica gel chromatography it was possible to obtain enantiopure **125**, which ran just ahead of the racemic material.



Scheme 27

With enantiopure alcohol **125** in hand conversion to (-)-epibatidine was performed using the slightly modified procedure of Broka (Scheme 4) to give the natural product in 9 steps and an overall 25% yield (Scheme 28).

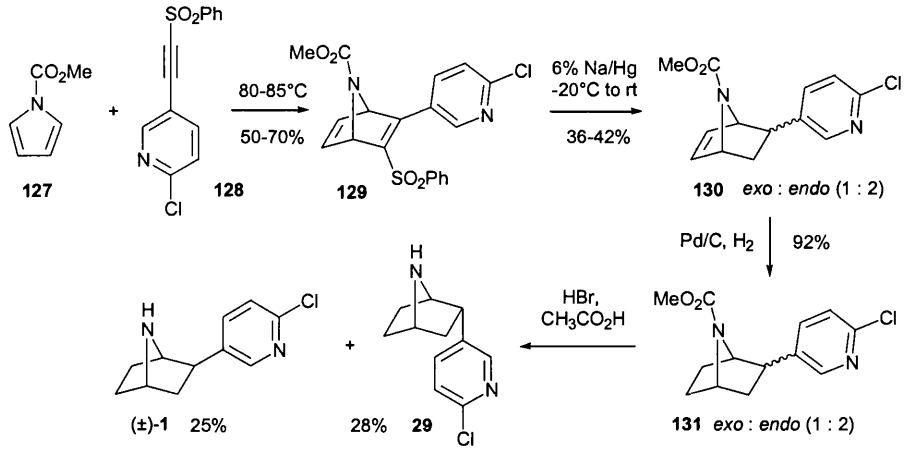


Scheme 28

The synthesis was selective, with a high degree of enantioselectivity in the protonation step although overall the synthesis was somewhat over long.

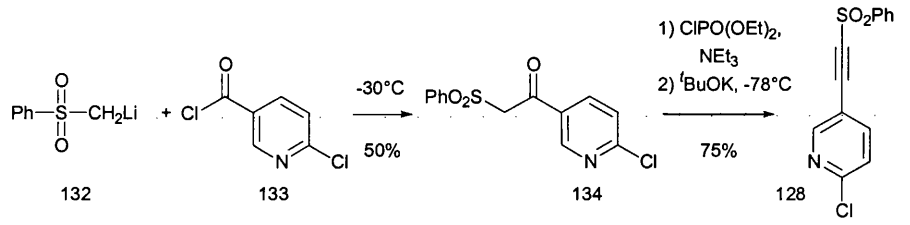
2) Synthesis via coupling of aryl substituent to aza[2.2.1]bicycle

The first synthesis of epibatidine to use a Diels-Alder reaction with pyrrole to construct the aza[2.2.1]bicyclic framework was reported by Shen and Huang in early 1993 (Scheme 29).[32] Previous acetylene dienophiles had been demonstrated in this reaction with carbamate pyrrole **127** but were much less efficient than pyridyl acetylene **128** prepared by Shen *et al.* Adduct **129** was attained in good yield. Reduction of the sulphone was carried out using standard amalgam conditions. The yield was poor and the reaction was not specific, a 2:1 mixture of *endo:exo* pyridine isomers was formed, with the undesired *endo* isomer being the major product. Hydrogenation of the double bond and carbamate cleavage with HBr in acetic acid provided epibatidine and its *endo* isomer **29**. No attempt to epimerise *endo* epibatidine **29** was made by this group (no literature on this transformation had been published at the time). Shen and Huang also resolved racemic epibatidine successfully into its enantiomeric forms using tartaric acid.



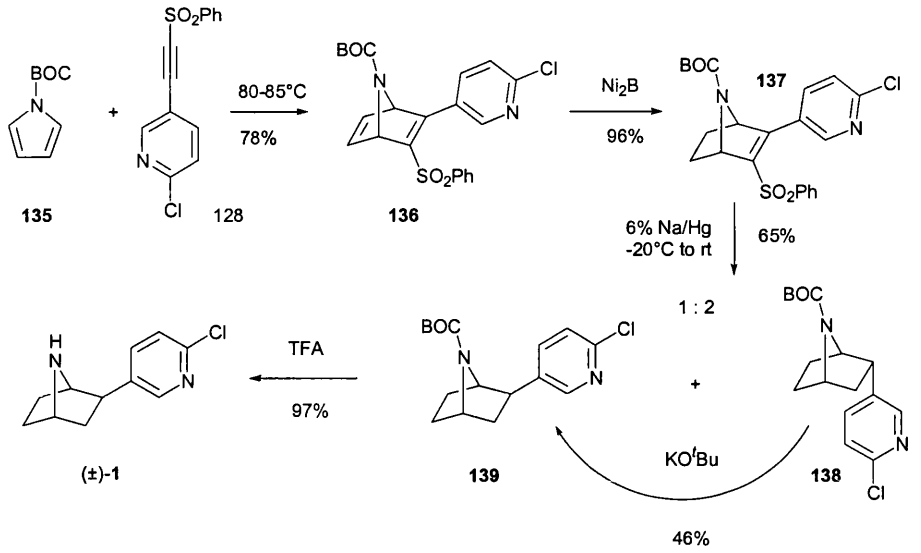
Scheme 29

The pyridyl acetylene **128** was prepared from the ketone **134** (Scheme 30) (the β-keto sulphone **134** was prepared from **132** and **133** in a 50% yield). Phosphorylation and then ^{t}BuOK-induced elimination produced the desired acetylene.



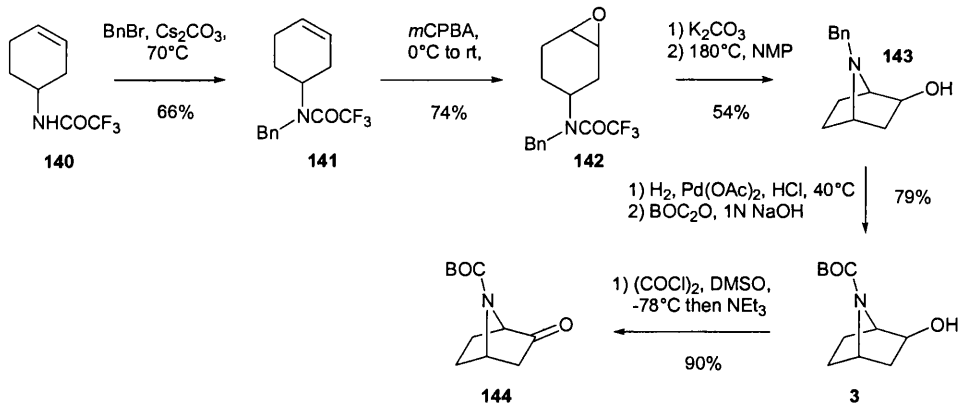
Scheme 30

Two years later Carroll and Kotian disclosed a modified version of the Shen synthesis in an attempt to address its shortcomings (Scheme 31).[33] By changing protecting groups, BOC pyrrole **135** was reacted with the activated acetylene in an improved 78% yield to form adduct **136**. Nickel boride was used to reduce the unsubstituted double bond before the amalgam reduction of the vinyl sulphone. This was achieved in significantly higher yield than before but still with the undesired *endo* isomer **138** formed in preference to *exo* **139**. With the epimerisation chemistry now known, the *endo* isomer **139** was converted, albeit in low yield, to *exo* **139**. The carbamate cleavage with TFA to yield epibatidine was affected in an excellent 97% yield. The deprotection step represented a significant improvement in efficiency over Shen's conditions for the cleavage of the methyl carbamate.



Scheme 31

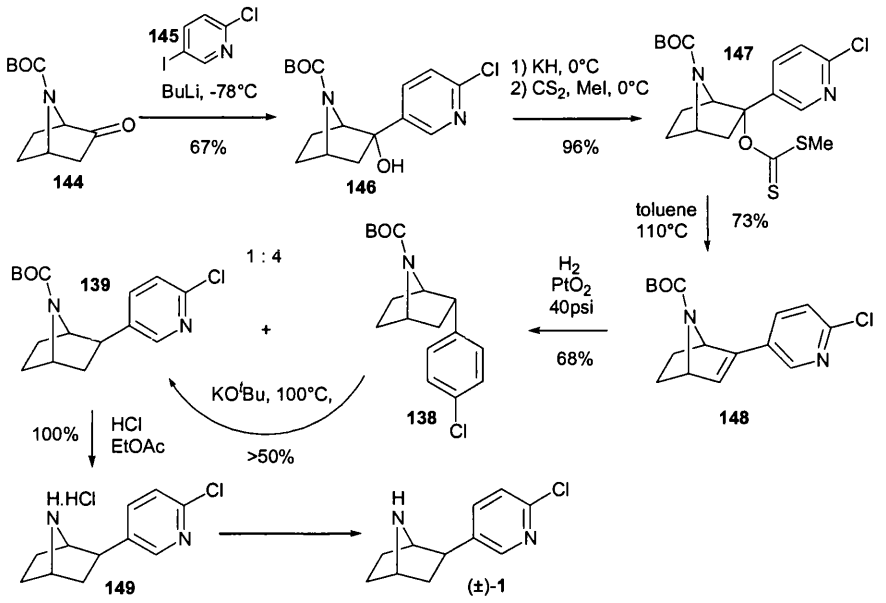
A synthesis that did not use Diels-Alder chemistry to construct the aza[2.2.1]heptane skeleton was published later in 1993 by Fletcher and co-workers.[6, 34] Their construction of the bicyclic ring structure involved an internal nucleophilic epoxide opening of protected amino cyclohexane **142** to give hyroxylated bicycle **143** (Scheme 32). The protected amine was prepared in two steps from alkene **140**. Benzylation, followed by epoxidation gave **142** as a 2.5:1 mixture of *trans*:*cis* stereoisomers in 74% yield. Hydrolysis and cyclisation in the presence of *N*-methyl pyrrolidinone gave exclusively the unexpected *exo* alcohol adduct **143** in 61% yield. A protecting group conversion from benzyl to BOC was achieved in 79% yield and under Swern conditions the alcohol **3** was oxidised to the ketone **144** in high yield.



Scheme 32

Treatment of **144** with lithiated chloropyridine derived from iodopyridine **145** gave exclusively the *exo* addition product **146**. Dehydration was carried out by formation and subsequent thermolytic cleavage of *S*-methyl xanthate **147** in an overall yield of 70%. Hydrogenation of the resultant alkene produced a 4:1 mixture of epimers **138** and **139** in a 68% yield but the undesired *endo* adduct **139** was the major product. Epimerisation of *endo*-**138** to *exo*-**139** was achieved with KO^{t}Bu in ^{t}BuOH at reflux to form a greater than

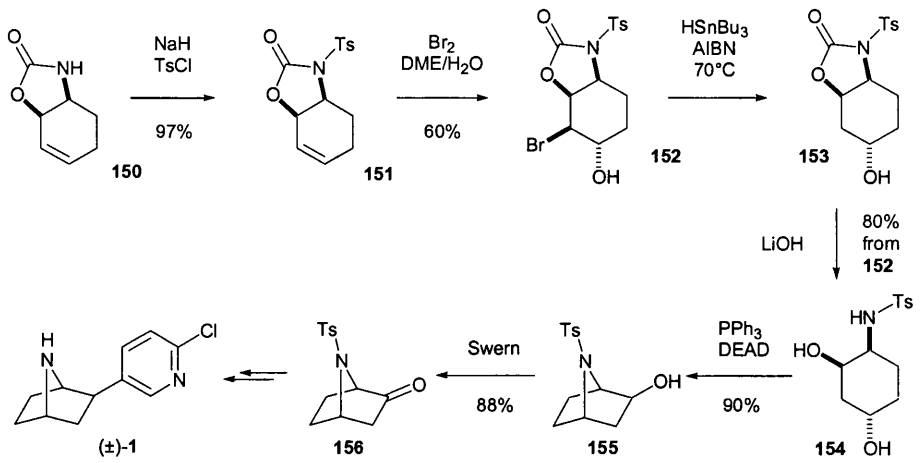
50% overall yield of the desired *exo* adduct. Cleavage of the carbamate protecting group was achieved in quantitative yield by treatment of carbamate **139** with HCl in ethyl acetate to yield racemic epibatidine.



Scheme 33

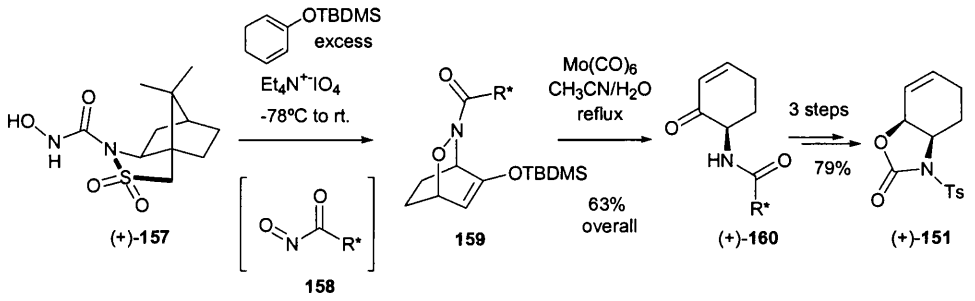
This synthesis demonstrated the first use of ketone **144** as useful intermediate in the synthesis of epibatidine. The reduction of the alkene **148** was the main weakness as it prepares the undesired *endo* isomer **138** as the major product. Successful epimerisation to the desired *exo* isomer was achieved but this transformation was low yielding.

Royer *et al.* published a racemic synthesis of epibatidine in 1998 that prepared the tosyl ketone **156**, then a known epibatidine intermediate *via* a diastereoselective bromohydroxylation of an amino cyclohexene **151** (Scheme 34).[35] The synthesis began with the preparation of cyclohexene **151** from oxazolidinone **150** (prepared from cyclohexadiene in four steps in 47%). Treatment of the tosylate with bromine in DME/H_2O gave two diastereomers in a 4:1 ratio, the major product being the desired isomer **152** isolated in a 60% yield. The extraneous halogen atom was removed under radical conditions and the oxazolidinone ring was hydrolysed to give alcohol **154** in an 80% yield. Cyclisation was performed using Mitsunobu conditions to provide bicycle **155** in an excellent 90% yield. Oxidation to the ketone **156** was achieved under Swern conditions. This ketone was already a known intermediate in Natsume's synthesis of epibatidine (Scheme 43).



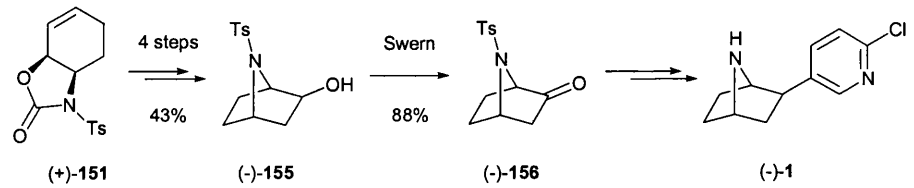
Scheme 34

In 2000 Royer and co-workers reported another enantioselective synthesis based on the strategy of Johnson, a nitroso Diels-Alder cycloaddition.[36, 37] They employed hydroxamic acid (+)-**157**, derived in one step from (+)-camphorsultam as their chiral starting material (Scheme 35). *In situ* oxidation gave the dienophile nitroso species **158** which cyclised with 2-OTBDMS cyclohexadiene to yield a single adduct **159**. This compound was unstable and was therefore converted crude, to the enone (+)-**160**, as a single diastereomer in 63% yield from hydroxamic acid (+)-**157**. Enone (+)-**160** was converted in three steps to carbamate (+)-**151**.



Scheme 35

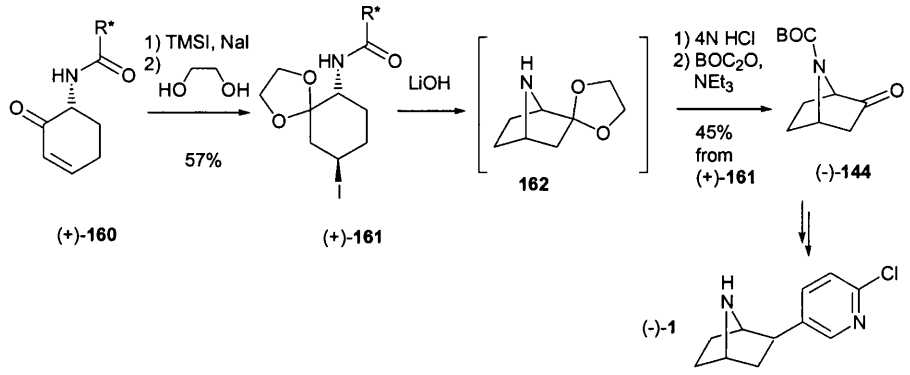
Carbamate (+)-**151** was then converted to (-)-epibatidine using the previously reported chemistry (Scheme 36) and the work of Natsume and Okabe (Scheme 43), *via* ketone (-)-**156**.



Scheme 36

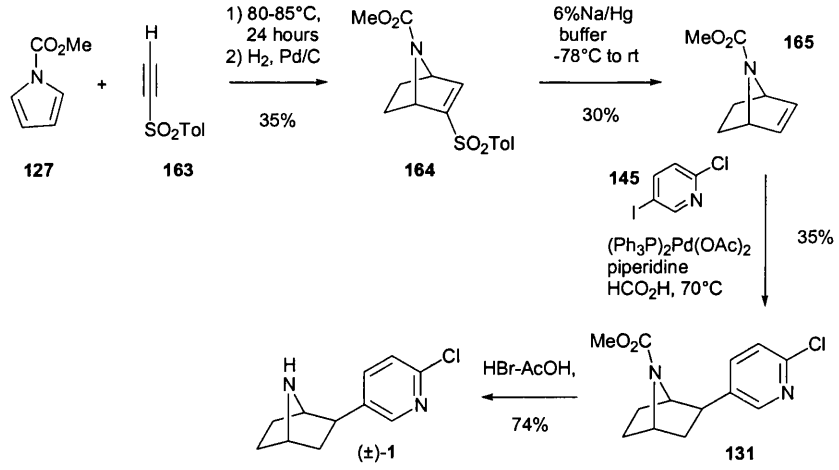
Royer and co-workers later improved their synthesis by preparing the BOC protected ketone (-)-**144** in four steps from the enantiopure enone (+)-**160** (Scheme 37). Iodination followed by ketalisation provided iodide (+)-**161** in a 57% yield. Base induced cyclisation followed by *in situ* cleavage of the acetal and BOC

protection of the free amine gave ketone (-)-**144**. Conversion of this ketone to epibatidine was known *via* the chemistry of Trudell (Scheme 47) or Fletcher (Scheme 33).



Scheme 37

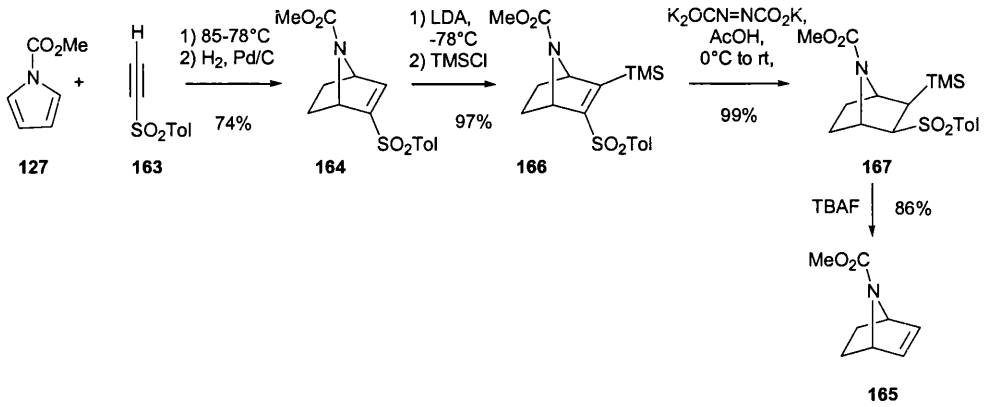
In 1993 Clayton and Regan reported a second synthesis of epibatidine that used a Diels-Alder reaction to construct the core aza[2.2.1]bicycle structure (Scheme 38).[38] It is one of the shortest and most convergent syntheses published to date, but suffered from several low yielding steps. The synthesis proceeded with the Diels-Alder reaction of protected pyrrole **127** and tosylated acetylene **163** to prepare the bicyclic structure of the natural product in one step. Hydrogenation of the unsubstituted double bond gave vinyl sulphone **164** in a 35% yield from the acetylene **163**. Amalgam reduction of the sulphone provided the alkene **165** in a 30% yield. Reductive Heck arylation conditions using iodo-chloro pyridine **145**, gave exclusively the *exo* adduct **131** in a 35% yield. Carbamate deprotection was then achieved with HBr in acetic acid to give (±)-epibatidine in 74% yield.



Scheme 38

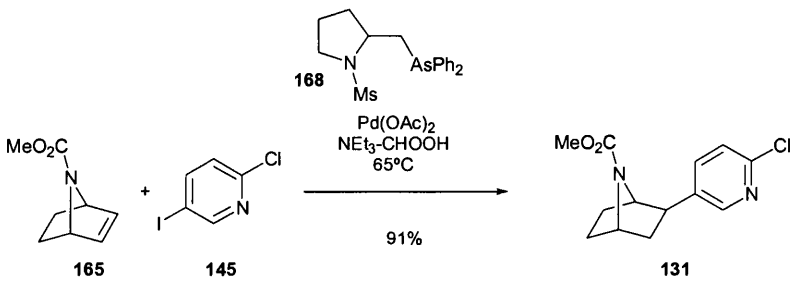
This short and convergent route inspired Kaufmann and co-workers who attempted to optimise its efficiency by improving the yield for the preparation of the alkene intermediate **165** (Scheme 39).[39] It was found that by maintaining careful control of the temperature, the initial Diels-Alder reaction could be carried out with an improved 74% yield. (Alternative conditions, using high pressure, 12kbar, improved the yield to 81%.) The second troublesome step of Clayton and Regan's synthesis was the elimination of

the sulphone group under reductive conditions. Kaufmann's group also struggled to achieve reproducible higher yields for this transformation and sought a different β–elimination method to remove the sulphone. Saturated silylated sulphone **167** was prepared in two very efficient steps from the hydrogenated Diels-Alder adduct **164**. Firstly, selective deprotonation with LDA, then quenching of the anion with TMSCl gave vinyl silane **166**. Reduction with complete *endo* selectivity was achieved with diimide in virtually quantitative yield. Treatment of silyl sulphone **167** with an excess of TBAF gave the alkene **165** cleanly as the sole product in 86% yield.



Scheme 39

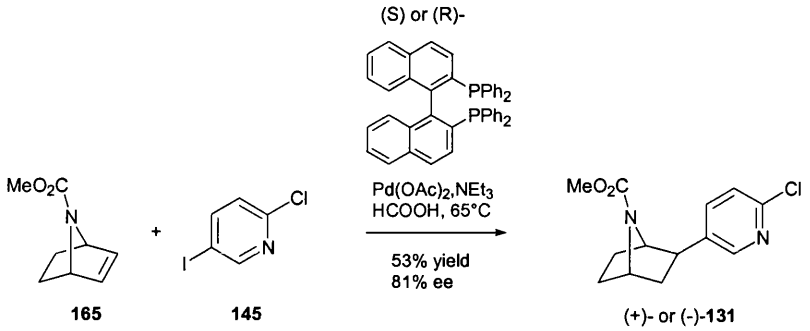
With the improved procedure for the preparation of the alkene in hand, Kaufmann and co-workers looked to improve the efficiency of the reductive Heck coupling to add the chloro-pyridine moiety. The use of arsine ligands in place of phosphine ligands was found to greatly improve the yield of the coupled product **131**. The replacement of triphenyl phosphine with triphenyl arsine increased the yield of bicycle **131** in the Heck reaction from 45% to 81%.[40] In their attempts to produce an enantioselective coupling, Kaufmann and co-workers prepared ligand **168** (Scheme 40) a novel chiral arsine ligand derived from *S*-prolinol. Unfortunately it was not successful at inducing enantio-enriched products (only 11% ee) but it did improve the yield of pyridine **131** to 91%, the highest obtained. Using this procedure, racemic epibatidine was now obtainable in an impressive 59% overall yield from *bis*(trimethylsilyl)acetylene (the starting material for sulphonated acetylene **163**).



Scheme 40

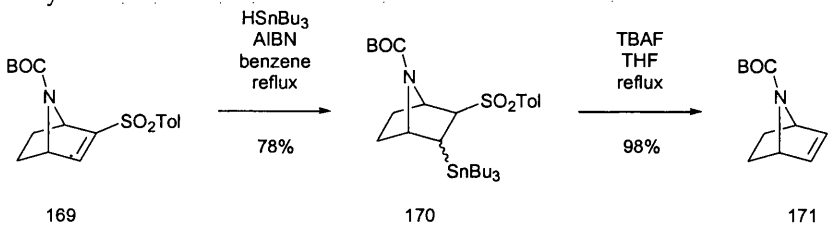
Still desiring an enantioselective synthesis of epibatidine *via* their route, chiral ligands were screened in the Heck reaction to produce enantioenriched adduct **131**. The best result from their studies was obtained

using BINAP in THF (Scheme 41).[41] Using this diphosphine either enantiomer of **131** could be prepared depending on the choice of (*R*)- or (*S*)- BINAP, in a moderate 53% yield and high enantioselectivity, 81% ee.



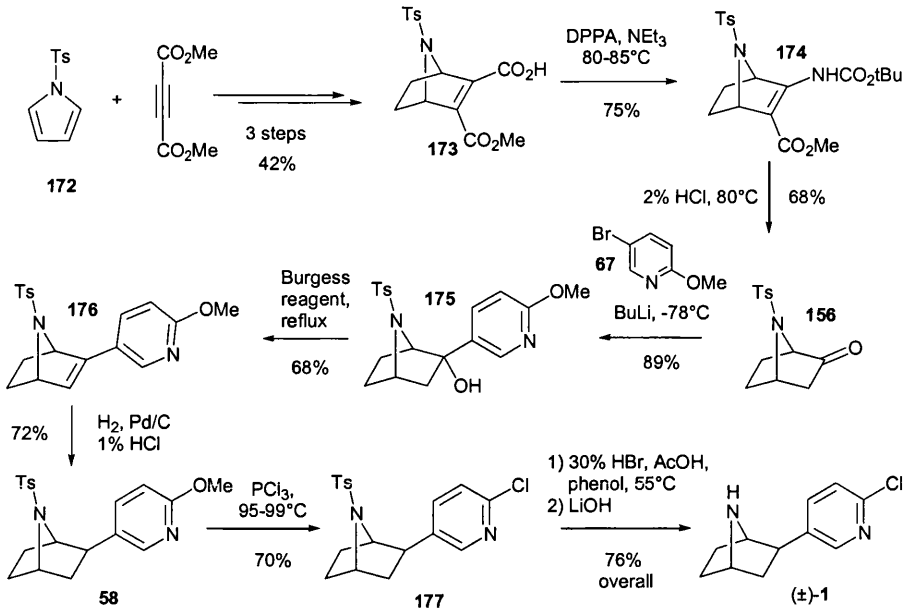
Scheme 41

Carroll and co-workers published a further modification to the Clayton and Regan synthesis in 1998.[42, 43] Choosing to use the more readily cleavable BOC carbamate as the pyrrole protecting group, Carroll used a novel hydrostannylation methodology to cleave the vinyl sulphone **169** to alkene **171** in two simple steps (Scheme 42). First the vinyl sulphone **169** was treated with $HSnBu_3$ and AIBN in benzene at reflux to give stannyl-sulphone **170** in 78% yield. Reaction of the stannane with TBAF in THF at reflux afforded the alkene **171** in 98% yield.



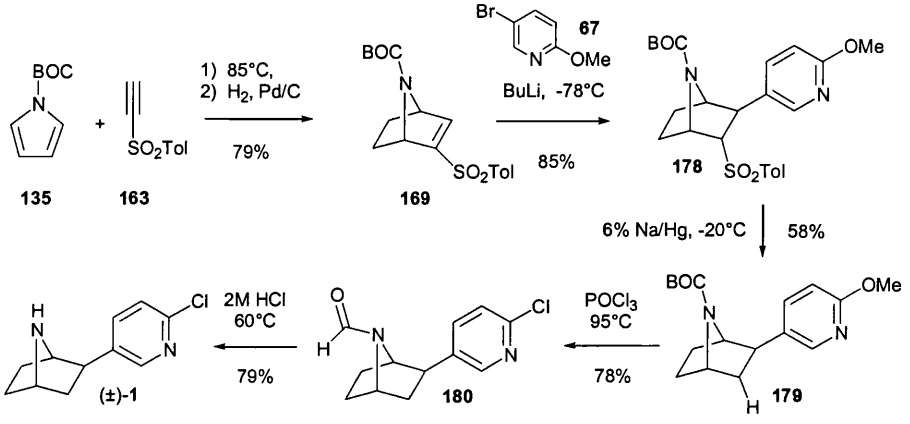
Scheme 42

Another early use of a protected pyrrole in a Diels-Alder reaction to construct the bicycle was reported by Natsume and Okabe in 1994 (Scheme 43).[44] Tosylated pyrrole **172** was reacted with DMAD,[45] hydrogenated and then hydrolysed with one equivalent of LiOH, to give tosylated monoester ester **173** in an overall 42% yield. The acid was treated with DPPA and heated to give the Curtius rearranged carbamate **174**. When treated with acid in a dioxane/H_2O solution at 80°C, **174** was readily converted into the ketone **156** in high yield. Coupling with lithiated methoxy pyridine **67** gave exclusively the *endo* alcohol **175**. Dehydration to give alkene **176** was performed using the Burgess reagent and hydrogenation in the presence of acid gave a 69% yield of the *exo* methoxypyridine **58**. Conversion of the methoxy group to the chloride was achieved with $POCl_3$ in DMF and cleavage of the tosyl group gave (±)-epibatidine in good yield. Like several other groups, Okabe and Natsume were forced to use methoxy pyridine in their synthesis and install the chlorine atom at the completion of their synthesis, due to the sensitivity of the chloro pyridine moiety to reduction under hydrogenation conditions.



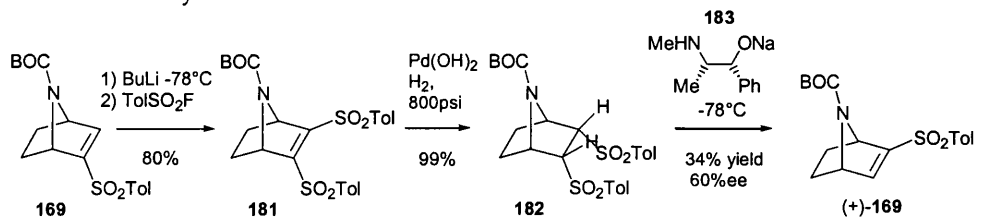
Scheme 43

In 1997 Simpkins and co-workers disclosed another synthesis using a pyrrole cycloaddition reaction.[46, 47] Their synthesis utilised a Michael addition reaction to carry out the key aryl coupling (Scheme 44). The synthesis began with the cycloaddition of BOC-protected pyrrole **135** with tosylated acetylene **163** and subsequent hydrogenation of the initial Diels-Alder adduct to yield vinyl sulphone **169** in 79% yield. Treatment with the lithiated pyridine species derived from the reaction of pyridine **67** and BuLi gave Michael adduct **178** as a single *exo* diastereomer. No *endo* adduct products were formed in the Michael addition reaction. Reductive elimination of the sulphone to form carbamate **179** was achieved in a 58% yield with sodium amalgam. Vilsmeier conditions converted the methoxy substituent into the required chloro substituent accompanied by concomitant BOC deprotection and *N*-formylation to yield formamide **180**. (The Michael addition of the chloro-pyridine addition was successful, but under reducing conditions to cleave the sulphone, concomitant reduction of the chlorine always accompanied the desired reaction.) Epibatidine was obtained with acid treatment of **180** in 79% yield completing this short and highly efficient synthesis.



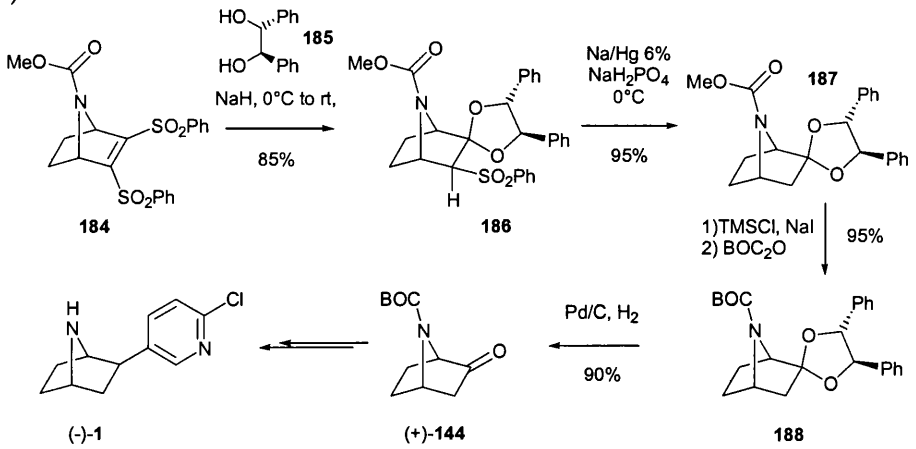
Scheme 44

To produce an enantioselective synthesis of epibatidine, Simpkins and co-workers looked to the enantioselective preparation of the Michael addition precursor vinyl sulphone **169**.[48] To achieve this aim, a novel chiral base mediated desymmetrisation reaction was attempted from symmetrical *bis* sulphone **182** (Scheme 45). The symmetrical *bis* sulphone was prepared from racemic **169** with a selective lithiation and trapping of the anion with tosyl fluoride to yield *bis* vinyl sulphone **181**. High-pressure hydrogenation afforded symmetrical **182** in 30-40% yields with 45-55% recovery of **181**. Conversion of *bis* sulphone **182** to enantioenriched vinyl sulphone **169** was attempted with a range of chiral bases derived from ephedrine. The most selective base **183**, gave the vinyl sulphone (+)-**169** in low yield and 60% ee. Vinyl sulphone (+)-**169** can be converted into (-)-epibatidine using the chemistry outlined in Scheme 44 above and represented a new enantioselective synthesis.



Scheme 45

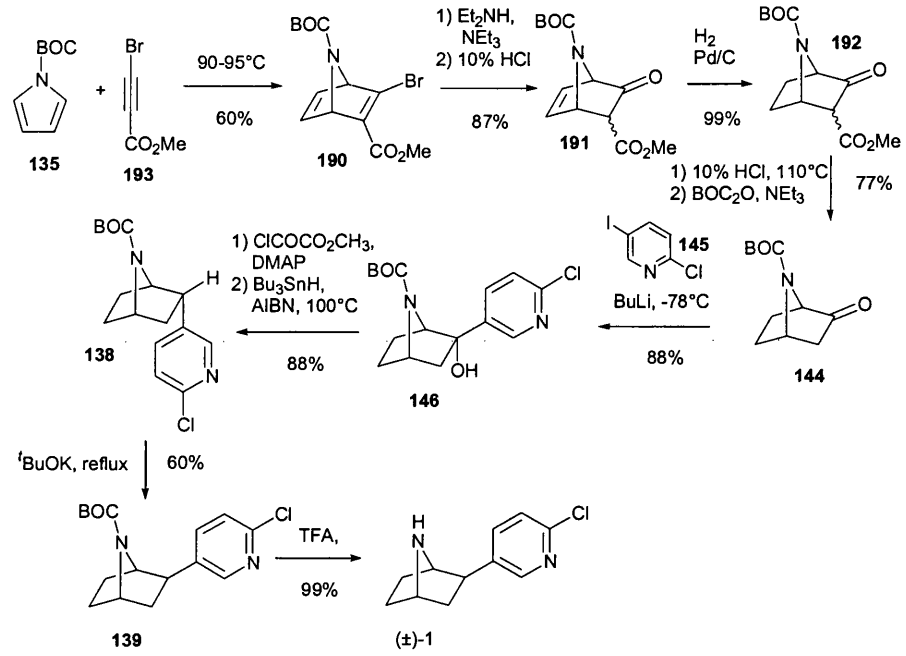
A desymmetrisation strategy to provide an enantioselective synthesis was also attempted by Pandey and co-workers on vinyl *bis* sulphone **184** (Scheme 46) that was synthesised using the chemistry developed by Simpkins (Scheme 45).[49] The sodium salt of chiral diol **185** was added to *bis* sulphone **184** to give acetal product **186** in 85% yield. Reduction of the sulphone using sodium amalgam was very high yielding but removal of the acetal proved more difficult. Reaction of **187** with TMSI cleaved only the carbamate protecting group and the free amine was reprotected as its BOC derivative **188**. Acetal removal was achieved by hydrogenation to give ketone (+)-**144** in a 90% yield. Ketone (+)-**144** was a known intermediate and can be converted to (-)-epibatidine, by the chemistry of Trudell (Scheme 47) or Fletcher (Scheme 33).



Scheme 46

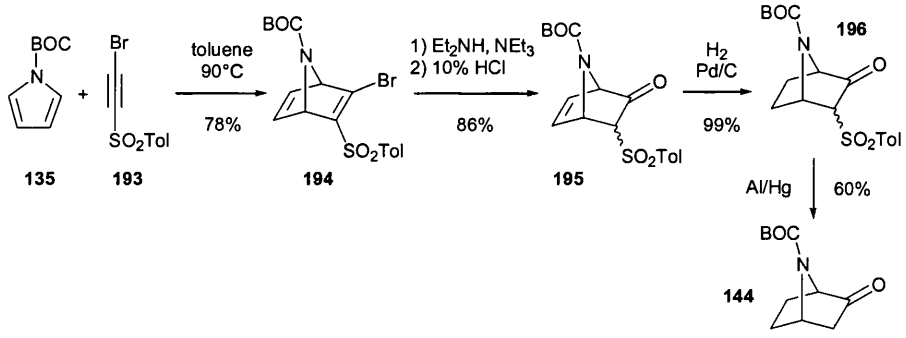
A pyrrole Diels-Alder reaction with methyl 3-bromopropiolate **189** was used by Trudell and co-workers in his first published synthesis of epibatidine (Scheme 47).[50] The cycloaddition reaction provided bicyclic

adduct **190** in good yield. Hydrolysis of the vinyl bromide gave ketone **191** as a mixture of isomers (7:1, *endo*:*exo*). Attempts to decarboxylate directly from alkene **191** with HCl at 100°C failed due to competing retro Diels-Alder reaction. Hydrogenation gave keto-ester **192** that underwent decarboxylation, using Rapoport's conditions to the ketone **144**.[51] Treatment of pyridine **145** with BuLi gave a lithiated aryl that adds selectively to ketone **144** to give *exo* pyridyl **146**. Deoxygenation of the tertiary alcohol was carried with the method of Dolan and McMillan and yielded the *endo* pyridyl **138** stereoselectively, in an 88% yield. This presents an improvement over conditions used for this transformation in previous syntheses (Schemes 33 and 43). Epimerisation to the desired *exo* isomer was achieved under vigorous basic conditions to give protected epibatidine precursor **139**. Cleavage of the BOC group was quantitative with TFA to provide racemic epibatidine.



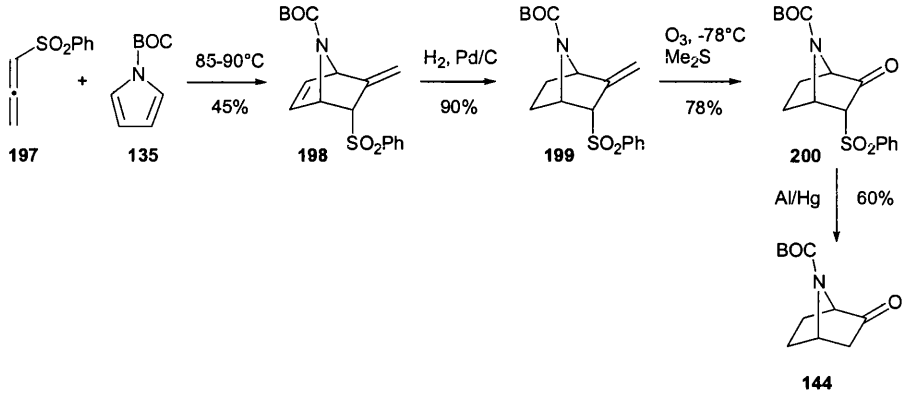
Scheme 47

Trudell and co-workers have also disclosed a similar synthesis utilising 2-bromoethynylsulphones the dienophile.[52] The advantage of this route comes mainly from the higher yields of the initial cyclisation step (Scheme 48). The decarboxylation reaction is replaced with an aluminium amalgam reduction of sulphone **196**, which provides the same intermediate ketone **144** as in Scheme 47 above.



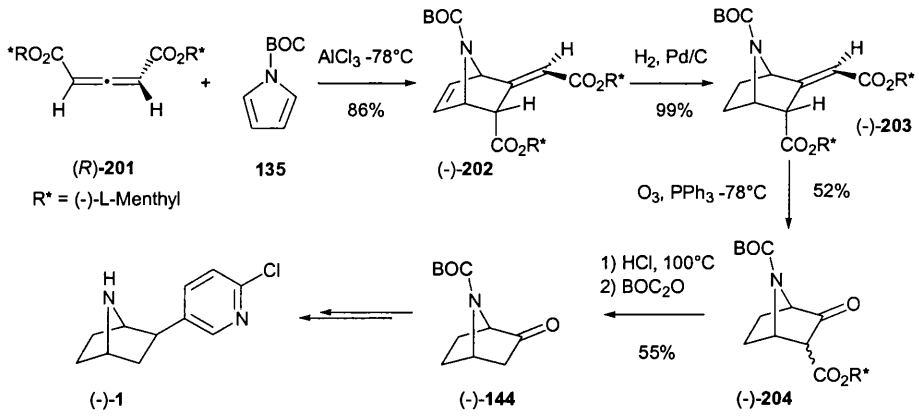
Scheme 48

A third method to prepare this ketone intermediate was also presented by Trudell's group (Scheme 49).[53] In this approach sulphonated allene **197** was used as a dienophile in a Diels-Alder cyclisation with BOC-pyrrole **135**. The reaction furnished vinyl adduct **198** as a single diastereomer in low yield. Regioselective hydrogenation of the cycloadduct gave *exo*-alkene **199** in high yield. Ozonolysis of the remaining double bond provided β-keto sulphone **200**, in 78% yield, which was then treated with aluminium amalgam to form ketone **144** in a 60% yield.



Scheme 49

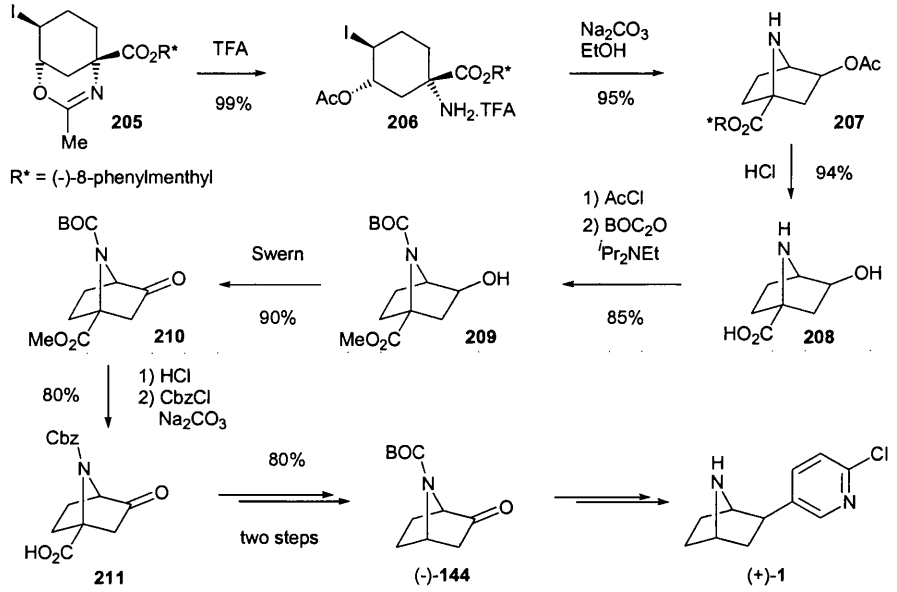
An enantioselective version of Trudell's allene synthesis of epibatidine has been reported by Node and co-workers (Scheme 50).[54] Enantiopure allene **201** was reacted with BOC-pyrrole in the presence of $AlCl_3$ at –78°C to give exclusively the *endo* adduct (-)-**202** in an 86% yield. Selective hydrogenation of the non-conjugated double bond provided alkene (-)-**203** in almost quantitative yield. Ozonolysis of the remaining double bond gave the β-keto ester (-)-**204** in moderate 52% yield. Decarboxylation of (-)-**204** under acid conditions and subsequent reprotection of the free amine gave ketone (-)-**144**. This compound is a known intermediate and can be converted to the natural (-)-isomer of epibatidine (Scheme 33 or 47).



Scheme 50

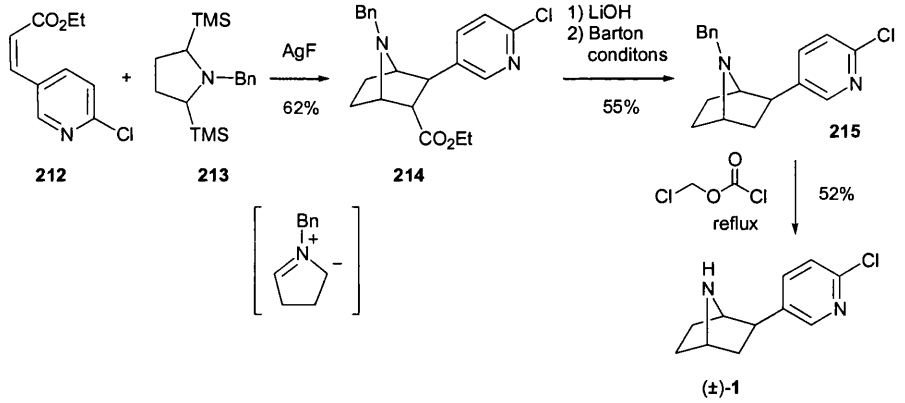
In 1999 another chiral auxiliary controlled Diels-Alder reaction to provide an enantioselective synthesis of epibatidine was disclosed by Avenoza and co-workers (Scheme 51).[55] 1,3 Oxazine **205** (formed by iodo-oxazination of Diels-Alder adduct of 8-phenylmenthyl 2-acetamidoacrylate with 1,3 butadiene) was

treated with TFA to yield ring opened salt **206**. Treatment with sodium carbonate then provided bicyclic amine **207** in an excellent 95% yield. Acid hydrolysis of the acetate and methyl ester then yielded alcohol **208** in high yield. BOC protection of the free amine and reformation of the methyl ester provided carbamate **209**. Swern oxidation conditions transformed the alcohol into ketone **210**. The BOC group was cleaved and replaced by the CBz group, (more stable to the decarboxylation chemistry) and the methyl ester was hydrolysed to the free carboxylic acid **211**. The conditions of Rapoport were used to decarboxylate acid **211** to form the ketone (-)-**144**.[51] The ketone was a known intermediate of epibatidine and can be converted to the (+)-enantiomer of the natural product *via* the chemistry of Trudell (Scheme 47), or Fletcher (Scheme 33).



Scheme 51

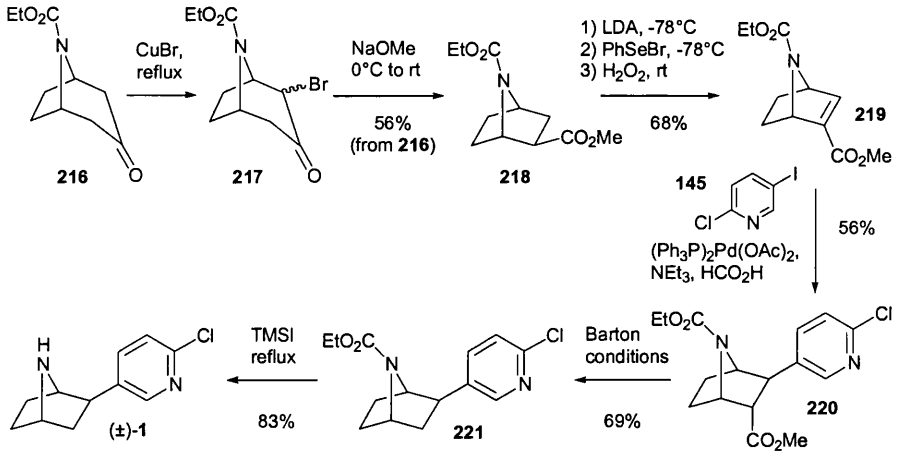
A different approach to the construction of the aza[2.2.1]bicycle was investigated in 1994 by Pandey *et al.* (Scheme 52).[56, 57] They prepared the core structure of epibatidine using a [3+2] cycloaddition strategy of *bis* silylated pyrrolidine **213** (prepared in 50% yield from BOC-pyrrolidine) and *cis* vinyl pyridine **212** (prepared from 6-chloropyridine-3-carboxaldehyde **24,** in 75% yield). Treatment of *bis* silane **213** with silver fluoride induces a sequential double desilylation to form an unstabilised azomethine ylide that reacts with the electron poor alkene **212** to produce the *exo* pyridyl adduct **214** in a 62% yield. Hydrolysis of the ester followed by decarboxylation, using the Barton protocol, gave benzylated epibatidine **215**. Deprotection with α-chloromethyl chloroformate in DCE and then MeOH gave the racemic natural product in 52% yield.



Scheme 52

3) Synthetic strategies derived from natural products and the chiral pool.

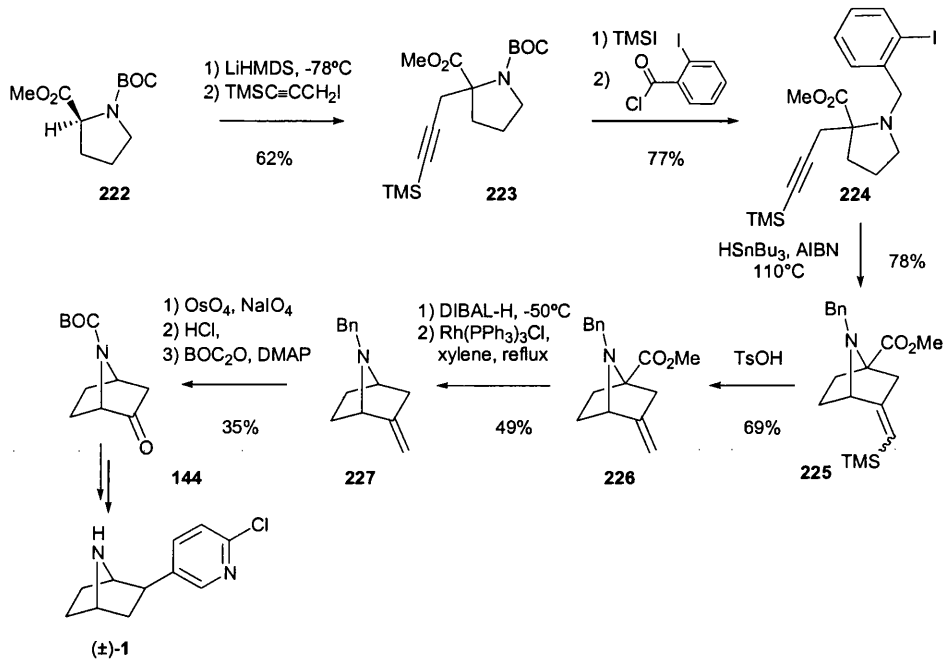
Bai and co-workers have published a synthesis of epibatidine that starts from readily available tropinone (Scheme 53).[58, 59] The key step of the synthesis involved a Favorskii type ring contraction to form the necessary [2.2.1] bicycle from the [3.2.1] bicyclic starting material. First, natural tropinone was converted to its carbamate derivative **216**. Treatment with CuBr in a mixture of $CHCl_3$ and EtOAc at reflux provided a 1:1 mixture of mono bromide isomers **217**. Without separation of these isomers, mixture **217** was exposed to NaOMe in DME at 0°C to yield the ester **218** in an overall 56% yield from the carbamate **216**. Lithiation, then quenching of the anion with PhSeBr followed by oxidative induced elimination of the selenide delivered unsaturated ester **219** in four days. Room temperature Heck coupling provided bicycle **220** as a single *exo-trans*-pyridyl isomer. Acid hydrolysis and Barton decarboxylation conditions gave carbamate **221**, which was deprotected with TMSI in $CHCl_3$ at reflux to yield (±)-epibatidine in good yield.



Scheme 53

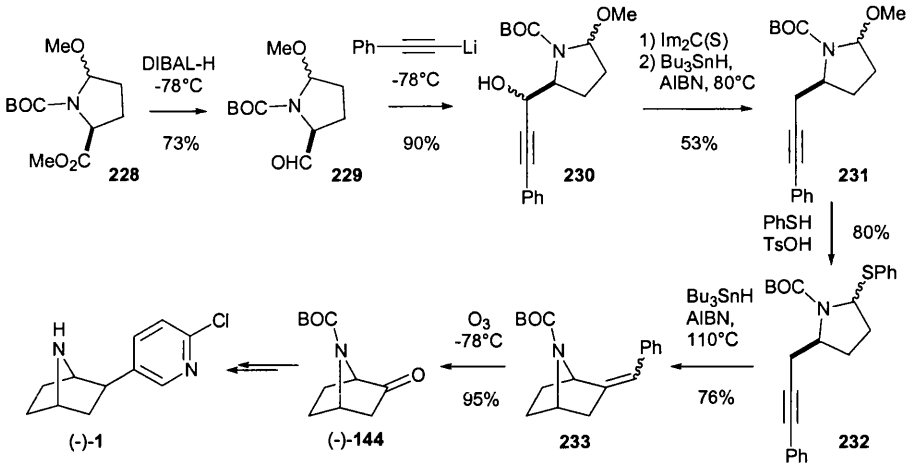
In 1997, Ikeda *et al.* reported a synthesis of racemic epibatidine that used *N*-protected (*S*)-proline derivative **222** as its starting point (Scheme 54).[60] The key step of their synthesis was the construction of the bicycle **225** from the *o*-iodo benzylamine **224** under radical conditions in an impressive 78% yield.

Benzylamine **224** was readily prepared from the protected glutamic acid derivative **222** in four steps in good yield. Acidic cleavage of the TMS group provided *exo* cyclic alkene **226**. Decarboxylation was achieved in a two-step process; first DIBAL reduction to the aldehyde followed by decarbonylation with the addition Wilkinson's catalyst. Oxidation of alkene **227** with OsO4, followed by cleavage with $NaIO_4$ and a protecting group conversion, gave known epibatidine intermediate, ketone **144**. The chemistry developed by Fletcher (Scheme 33) or Trudell (Scheme 47) can be used to convert the ketone **144** to epibatidine.



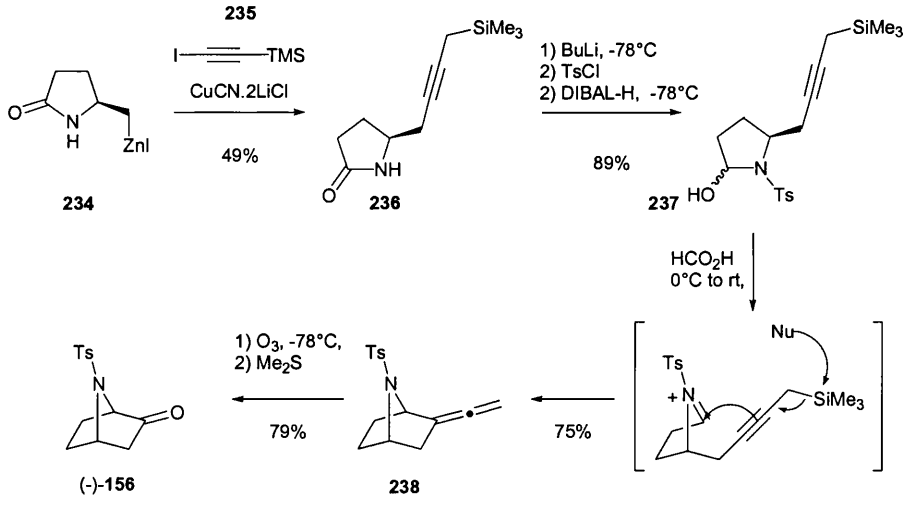
Scheme 54

In 1998 a stereocontrolled synthesis that also utilised a radical cyclisation to generate the bicycle was published by Clive and Yeh (Scheme 55).[61] (S)-pyroglutamic acid was converted to *N*-protected epimeric methyl ether **228** in four straightforward and high yielding steps. Reduction of the ester with DIBAL gave the aldehyde **229** in 73% yield. Treatment with lithiated phenyl acetylene provided a mixture of alcohols **230** in high yield. Deoxygenation of alcohol mixture **230** was performed in two steps, formation of xanthate ester followed by radical cleavage to give acetylene **231** in an overall 53% yield. Conversion of the methoxy group to thiophenyl group was accomplished in DCM with TsOH to afford radical cyclisation substrate **232**. Slow addition of $HSnBu_3$ and AIBN to a 110°C solution of sulphide **232** in toluene gave epimeric bicycle **233** in 76% yield. Conversion to known epibatidine intermediate, ketone (-)-**144**, was carried out by ozonolysis in excellent yield. (For conversion of ketone **144** to epibatidine see Schemes 33 and 47)



Scheme 55

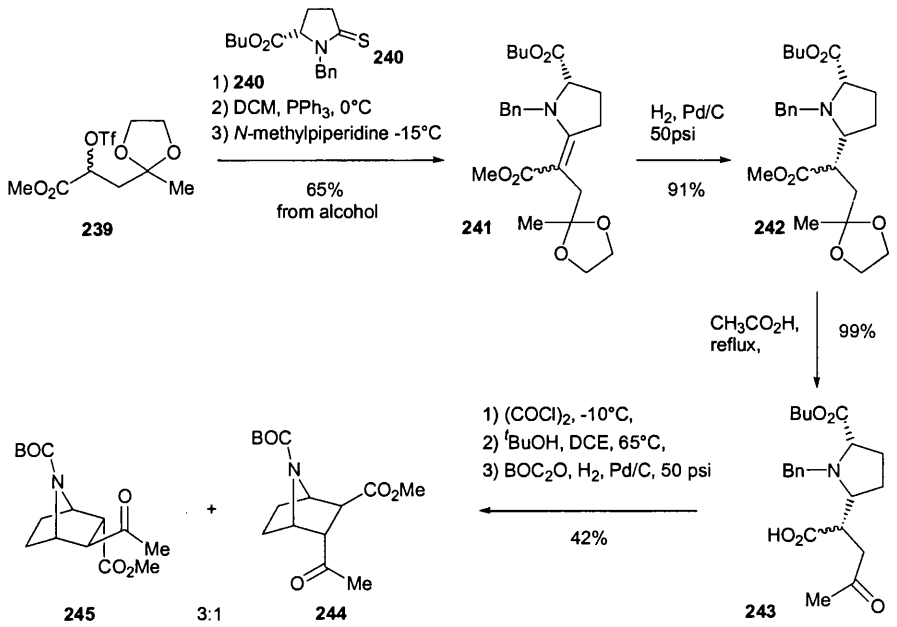
An alternative synthesis of the natural enantiomer of epibatidine starting from an (*S*)-pyroglutamic acid derivative was disclosed by Hiemstra and co-workers (Scheme 56).[62] Organozinc **234** is treated with iodo acetylene **235** and CuCN.2LiCl to give the coupled acetylene **236** in a moderate yield. Protection as the tosylate followed by DIBAL reduction of the carbonyl gave epimeric alcohol product **237** in an 89% yield. (Alternative protection as methyl or ^{t}butyl carbamate was also successful and these derivatives can also be converted to ketone analogs of **156**.) Clean cyclisation was carried out with formic acid at 0°C to give allene **238** in 75% yield. Treatment of the allene with ozone gave the enantiopure bicyclic ketone (-)-**156** a known intermediate of (-)-epibatidine. This can be converted *via* the chemistry of Okabe (Scheme 43) into the natural product.



Scheme 56

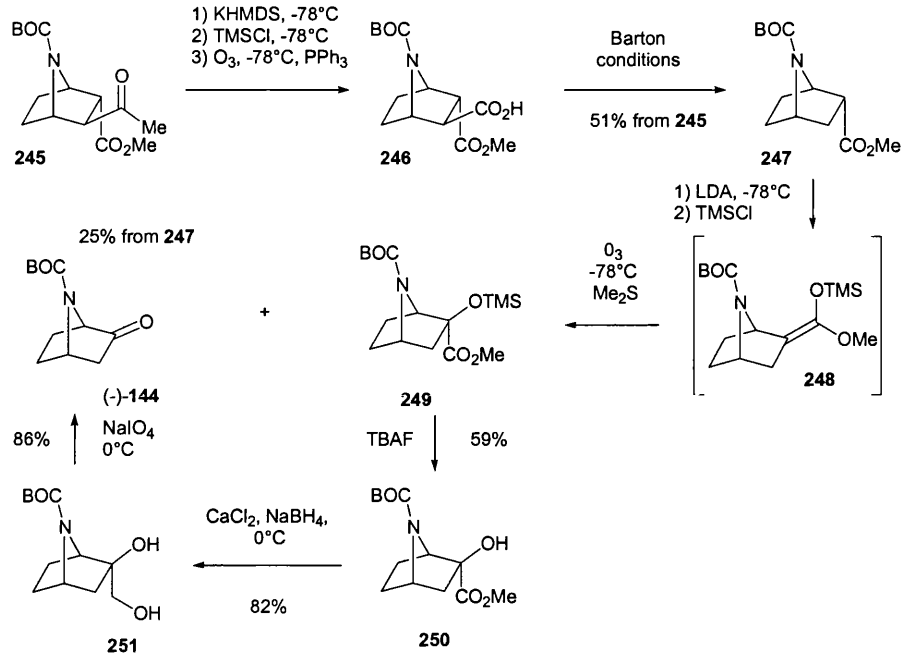
Rapoport and co-workers describe an enantioselective synthesis of either isomer of ketone intermediates (-)-**144** and (+)-**144** starting from L-glutamic acid and levelunic acid.[63] The route to the natural isomer is described in Schemes 57 and 58. Triflate **239** (prepared in 5 steps from levelunic acid) was treated with proline-derived thioester **240** to give vinyl ester **241** as a 6:5 mixture of diastereomers in a 65% yield from the alcohol (triflate precursor). Hydrogenation gave saturated epimeric *cis* pyrrolidine **242** in high yield.

Acid cleavage of the acetal and methyl ester yielded keto-acid **243**. Decarboxylation with oxalyl chloride provided an iminium ion that underwent intramolecular cyclisation to form a three to one mixture of bicyclic diastereomers that were reprotected as their BOC derivatives **244** and **245** in 42% yield.



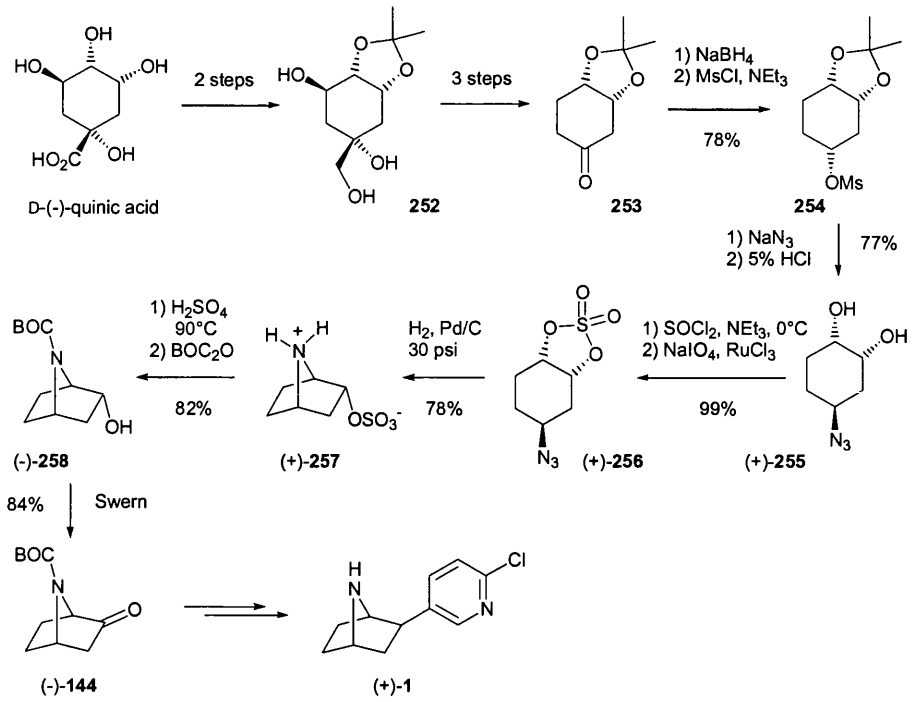
Scheme 57

Esters **244** and **245** can be converted to either enantiomer of ketone intermediate **144**. The route through to the natural enantiomer of the ketone intermediate is shown in Scheme 58. For clarity, just the *exo*-ketone **245** is shown, but its diastereomer **244** can also be converted to the ketone (-)-**144** using the same chemistry. Selective enolisation of the acetyl group and trapping with TMSCl gave a silyl enol-ether that was treated crude with ozone to produce acid **246**. Decarboxylation using radical conditions gave *endo* methyl ester **247** in an overall yield of 51%. Reaction of this ester with LDA and trapping the resultant enolate with TMSCl formed silyl ketene acetal **248** that was reacted without purification, with ozone, to give a mixture of desired ketone (-)-**144** and ester **249**. The ester product can be converted through to the ketone by a three-step sequence. Cleavage of the TMS group followed by reduction of the ester gave diol **251**. The diol was then cleaved oxidatively to give ketone (-)-**144** in the presence of $NaIO_4$.



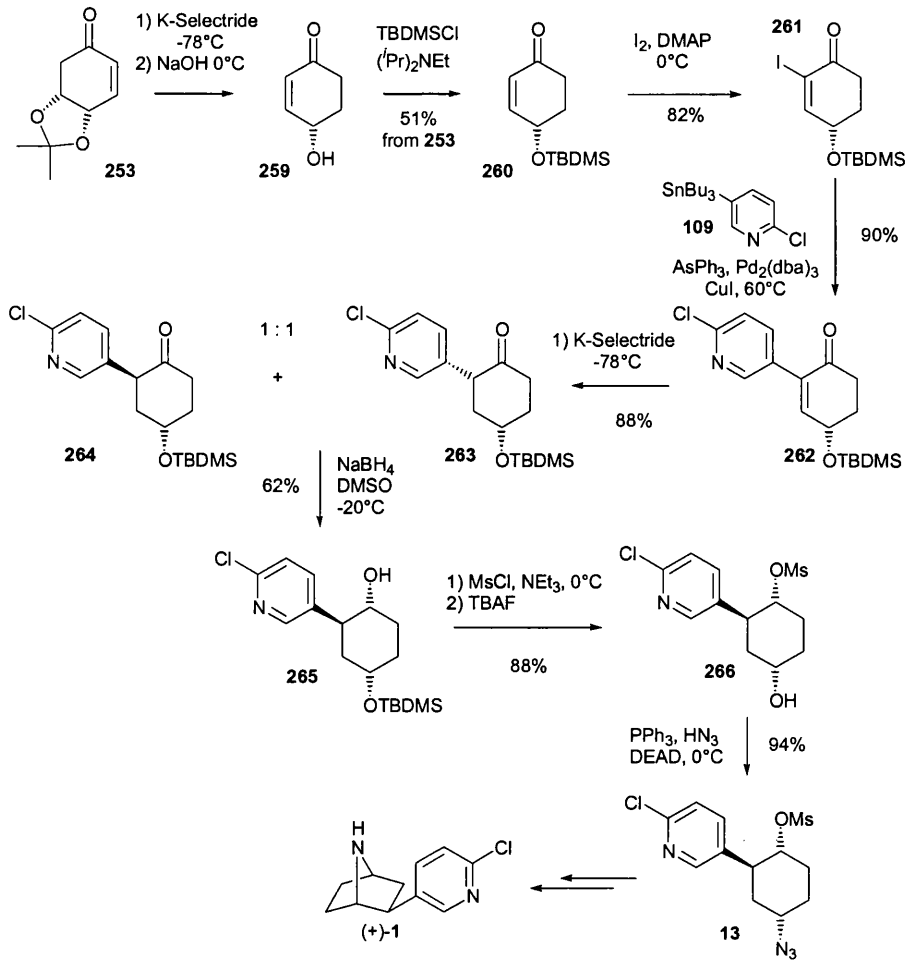
Scheme 58

A synthesis of the unnatural enantiomer of epibatidine using the chiral plant metabolite, quinic acid, as its chiral source has been described by Pollini and co-workers (Scheme 59).[64] Ketone **253** is readily available from D-(-)-quinic acid in five steps. The carbonyl was reduced and the resulting alcohol converted to its mesylate **254** in 78% yield. Displacement with sodium azide followed by acid hydrolysis of the acetal protecting group gave diol **255**. Treatment with $SOCl_2$ followed by oxidation gave cyclic sulphate **256** in almost quantitative yield. Reduction of the azide under hydrogenation conditions lead to amine formation and concomitant internal displacement to give bicycle (+)-**257**, which was isolated as its salt in 78% yield. Acid hydrolysis and protection of the free amine with a BOC group gave alcohol (-)-**258**. This was oxidised under Swern conditions to provide the known epibatidine intermediate, ketone (-)-**144**.



Scheme 59

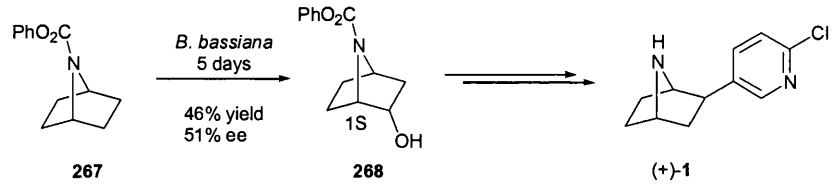
In 1999 a second synthesis of (+)-epibatidine starting from derivative **253**, of D-(-)-quinic acid was published by Barros *et al.* (Scheme 60).[65, 66] In their synthesis they followed the substituted cyclohexane strategy and prepared the Broka mesylate **14** in a stereo controlled synthesis. Protected alcohol **260** was prepared in 51% yield from acetal **253** in four steps. Selective α-iodination and subsequent Stille coupling of iodide **261** and stannyl pyridine **109** gave the coupled product **262** in excellent yield. Unfortunately reduction of the olefin produced ketones **263** and **264** in a 1:1 ratio. These proved impossible to separate and the mixture was reduced. Optimised conditions using DMSO as solvent gave the best yield of the desired diastereomer, alcohol **265** in 62%. Mesylation and cleavage of the silyl group provided alcohol **266** that was converted to the azide **13** using Mitsunobu conditions. From this compound (+)-epibatidine can be synthesised using either chemistry developed by Broka or Albertini (Schemes 4 and 11).



Scheme 60

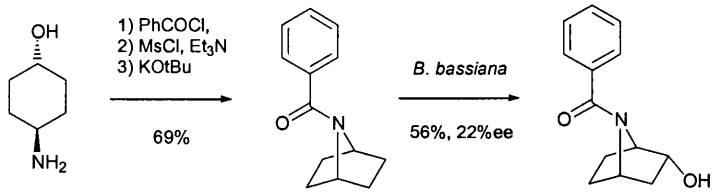
4) Enzymatic Syntheses of Epibatidine

There have been two reported syntheses of epibatidine *via* enzymatic methods. The first was disclosed by Davis and co-workers in 1997 (Scheme 61).[67] Protected azabicycle **267** was treated with *B. bassiana* in a fermentation tank over 5 days. A 46% yield of alcohol **268** was produced with 51% ee. Oxidation of alcohol **268** would provide ketone (+)-**144** and could be readily converted to the unnatural (+)-epibatidine enantiomer *via* the known chemistry of Trudell (Scheme 47) and Fletcher (Scheme 33).



Scheme 61

Olivio and Hemenway published an almost identical route, utilising the same enzyme a year later (Scheme 62).[68] Epibatidine would also be prepared from the ketone resulting from the oxidation of hydroxyl product **271**.



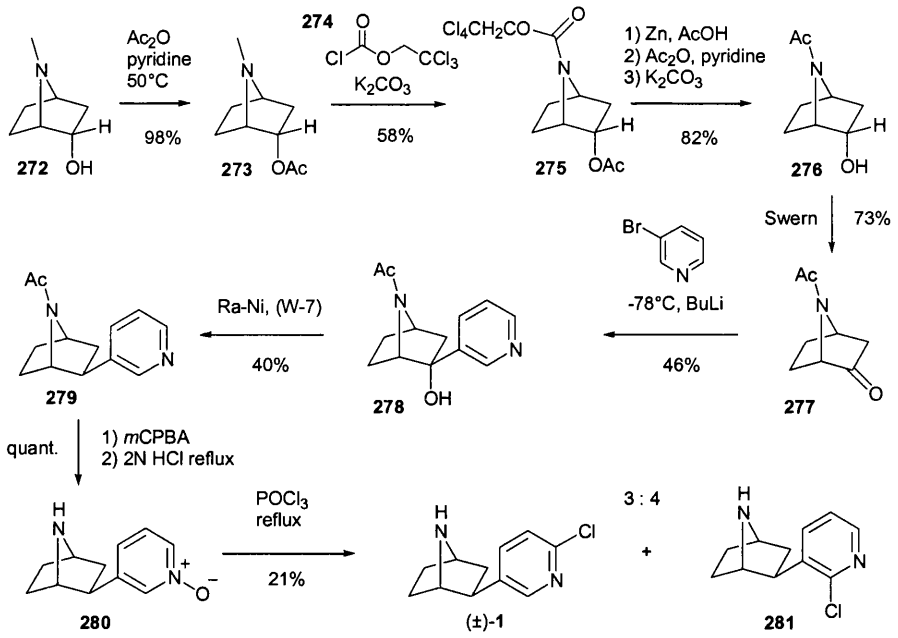
269 **270** **271**

Scheme 62

The two enzymatic procedures published to date are poor. They require the pre-construction of the synthetically challenging aza[2.2.1]bicyclic framework and provide alcohols with low efficiency in terms of both yield and enantioselectivity.

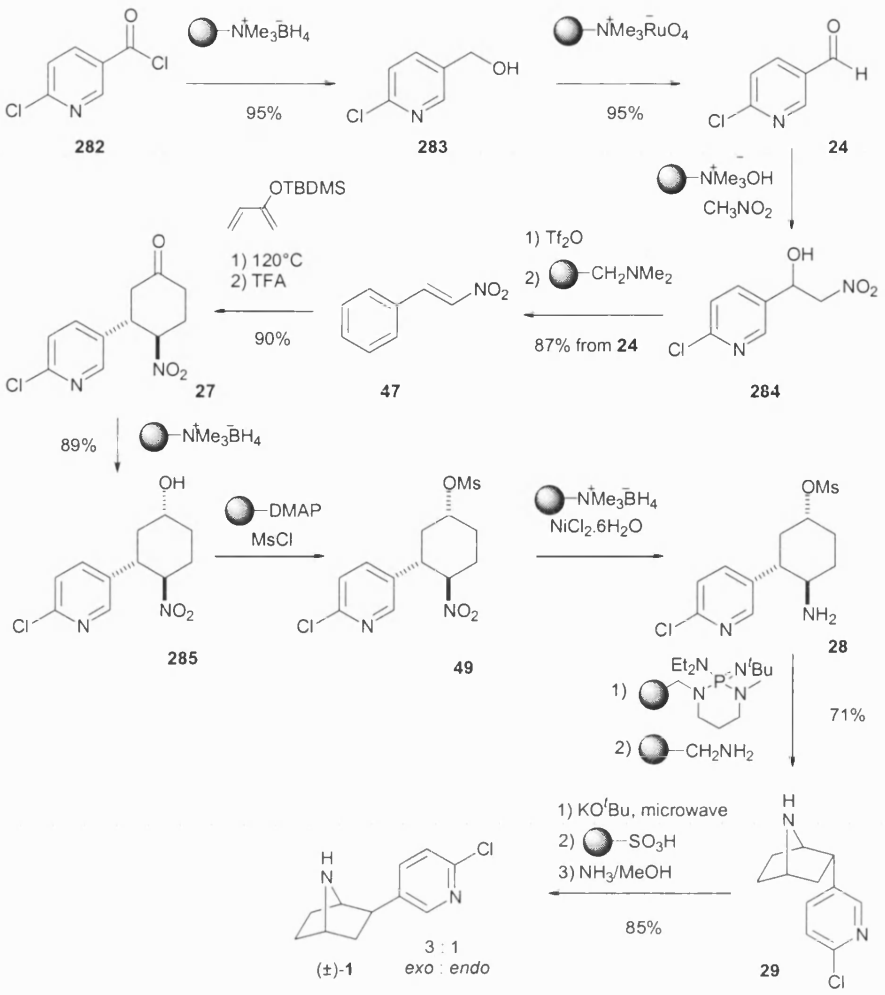
5) Miscellaneous syntheses

In 1994 Hakai and co-workers reported a synthesis of epibatidine from azabicyclo endo alcohol **272**, (prepared by the chemistry of Pfister *et al.*[69]) (Scheme 63).[70] The alcohol was protected to form acetate **273**, which was demethylated with 2,2,2-trichloroethyl chloroformate **274** to yield carbamate **275**. Conversion to the acetamide **276** was achieved in three steps in good overall yield. Swern oxidation of the alcohol afforded ketone **277** in 73% yield. Treatment with lithiated pyridine produced the *exo* pyridine adduct **278**. Reduction of the hydroxyl was carried out with Raney nickel, with retention of stereochemistry, to produce acetamide **279** in low yield. Oxidation of the pyridine and acid cleavage of the acetamide gave *N*-oxide **280**. Treatment with $POCl_3$ gave a mixture of epibatidine and chloro isomer **281** in a 3:4 ratio and 21% yield.



Scheme 63

Ley and co-workers disclosed a synthesis of racemic epibatidine using exclusively solid supported reagents and requiring no chromatographic purification (Scheme 64).[71] This was achieved using essentially the same synthetic sequence reported by Albertini *et al.* (Scheme 11). Commercially available acid chloride **282** was reduced to alcohol **283** with supported borohydride. A solid supported TPAP equivalent was used to oxidise the alcohol cleanly to the aldehyde **24**. Both steps provided products in an excellent 95% yield. Henry reaction with nitromethane gave alcohol **284**, which was converted crude to its triflate and then subjected to basic resin that promoted elimination to yield nitro alkene **47**. Diels-Alder reaction with 2-silyloxy butadiene and acid hydrolysis of the cycloadduct gave ketone **27** in 90% yield. A second solid supported hydride step gave alcohol **285** that was mesylated with the aid of solid supported DMAP to provide mesylate **49**. Reduction of the nitro group was achieved with borohydride with hydrated nickel and treatment of the resulting amine **28** with supported phosphazine base enabled the transannular cyclisation to form *endo* epibatidine **29** in high yield. The epimerisation step was partially successful, providing a 3:1 mixture of epimers, with epibatidine as the major product, in 85% yield



Scheme 64

Conclusions

There is some confusion in the literature over which enantiomer of ketone intermediates **144**, and **156** are converted to the natural enantiomer of epibatidine. Avenoza and Pollini report (+)-ketone is converted to (-)-epibatidine and Pandey, Node, Clive and Hiemstra report (-) ketone is converted to (-)-epibatidine. This may well stem from the initial confusion over the rotation of natural epibatidine, which has been reported as both positive and negative. Daly's initial biological paper with the results from his first trials with synthetic epibatidine stated that the natural isomer has a negative free rotation as the free base and a positive one when measured as its oxalate salt.[7] This was not clear from Fletcher and co-workers original paper on the absolute configuration of the natural product.[6]

The apparent Jeckyl and Hyde nature of the sensitivity of the chloro-pyridine moiety also presents some confusion. Shen, Fletcher, Kibayashi, Avenoza and Kitahara report no reduction of the chloride under hydrogenation conditions, using Pd/C, PtO_2, PtO_2, Pt/C and Rh/Al_2O_3 respectively. Shen and Carroll also report the successful use of Na/Hg amalgam reaction to reductively cleave a sulphone in the presence

of the chloro-pyridine moiety. Simpkins, Johnson and Natsume all report that concomitant reduction of the chloro-pyridine always accompanied hydrogenation with metal catalysis. Pandey does not report the reduction but his unusual choice of debenzylation conditions suggest the usual hydrogenation method had been problematic. Simpkins also notes the same concomitant reduction of the chloride accompanying the Na/Hg amalgam reduction conditions needed to reduce their sulphone. No reduction of the chloride has been reported under hydride or radical reducing conditions.

Of the racemic syntheses that employ the ring closure of a substituted cyclohexane, the most efficient and elegant is arguably that reported by Corey. The control exerted over the stereochemistry was impressive and the functional group conversion of the acid into the required amine was a succinct method of preparing the desired bicycle precursor.

However, the most successful and convergent racemic syntheses employ the Diels-Alder cyclisation reaction with a protected pyrrole to construct the aza[2.2.1]bicycloheptane skeleton. In particular those that follow the reductive Heck (Clayton and Kaufmann) and Michael addition (Simpkins) routes, demonstrate great efficiency. The complete *exo* selectivity of the coupling steps ensures that the low yielding epimerisation that is required in many syntheses is avoided. The overall yield of epibatidine, in the Kaufmann synthesis, is in an impressive 59% from the commercially available starting material, *bis*(trimethylsilyl)acetylene.

Of the enantioselective syntheses it is the catalytic examples that stand out. The Trost synthesis is arguably the best purely in terms of the yield and selectivity of his asymmetric allylic substitution desymmetrisation. The only drawback to the synthesis comes from how early in the synthetic sequence this selection occurs. Both enantiomers have to be taken separately through the remaining synthetic steps. The most convergent enantioselective synthesis comes from the work of Kaufmann. Both enantiomers of epibatidine can be made from an advanced alkene intermediate with high selectivity using the reductive Heck coupling reaction.

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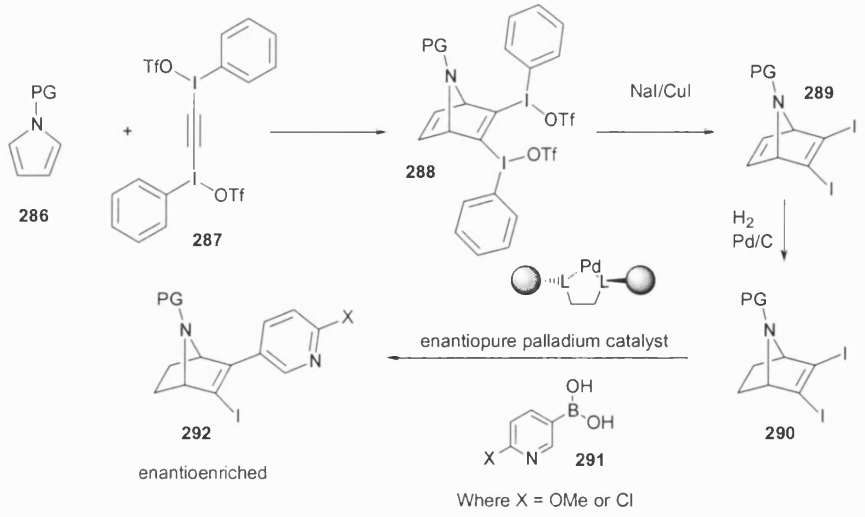
Introduction and background

The proposed synthetic route to enantiopure epibatidine

Despite the interest in the epibatidine structure and the many syntheses reported in the literature since its publication in 1992 there were surprisingly few enantioselective syntheses (not including those syntheses derived from the chiral pool or enriched *via* enzymatic resolution) reported at the outset of this project in 1998. Of the five already reported in the literature, Szantay (Chapter 1, Scheme 8)[1], Trost (Chapter1, Scheme 22),[2] Kibayashi (Chapter 1, Scheme 19),[3, 4] Kosugi (Chapter 1, Scheme 26)[5] and Simpkins (Chapter 1, Scheme 45)[6] none were wholly satisfactory. The Trost synthesis was the most efficient in terms of the selectivity and yields obtained in the enantio-discriminating step. However, this was the first step in the synthesis and both enantiomers were then taken separately through the rest of the synthetic sequence. Kibayashi's synthesis suffered from low yields in the key enantioselective reaction, as did the synthesis of Simpkins. Kosugi's enantioselective protonation process was an effective and selective reaction but the synthesis is long in terms of the numbers of steps involved. Szantay's ring closure was effective in terms of enantioselectivity but costly because it required five equivalents of an enantiopure chiral amine to achieve.

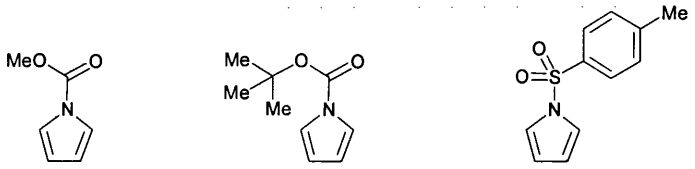
It was felt that there was definitely a need for a new, more efficient, catalytic, enantioselective synthesis of this intriguing compound. It should also be a flexible synthesis that would allow for the preparation of either enantiomer from a single intermediate near the end of the synthetic sequence. Due to the groups general interest in desymmetrisation chemistry and palladium coupling chemistry it was hoped to use diiodide **290** in a desymmetrising Suzuki-Miyaura coupling reaction with boronic pyridine **291** as the key enantioselective step of the synthesis (Scheme 1). Either enantiomer of the natural product (as well as a vast range of different aryl analogues) could then be synthesised from the vinyl diiodide **290** depending on the enantiomer of chiral catalyst chosen.



Scheme 1

The Diels-Alder cyclisation of protected pyrroles with activated acetylenes had already been shown to be a facile and efficient way to prepare the azabicyclo[2.2.1]heptane framework, by Clayton (Chapter 1, Scheme 38),[7] Simpkins (Chapter 1, Scheme 44),[8] Trudell (Chapter 1 Scheme 47)[9] and Natsume (Chapter 1, Scheme 43)[10] among others. It was hoped to extend this methodology to use activated acetylene **287** as the dienophile in the reaction.[11] This was very attractive; as it would allow for the formation of the desired diiodide **290** in just two steps from the Diels-Alder adduct **288**. Simple hydrogenation of the unsubstituted double bond and nucleophilic cleavage of the iodonium salts would then yield diiodide **290**.[12] The nucleophilic cleavage of the salt can also be carried out with copper bromide to give the dibromide analogue if required.

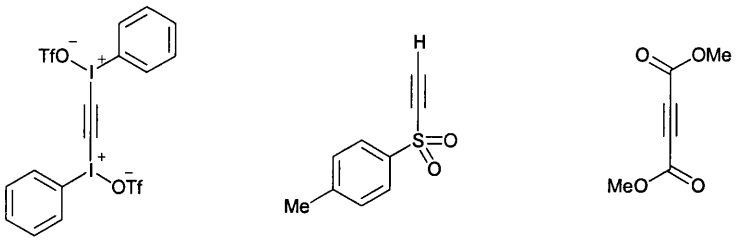
The Diels-Alder reaction between the acetylene **287** and pyrrole **286** would constitute a novel transformation. Acetylene **287**, though described as a dienophile "par excellence" when it was first published by Stang *et al.* has only been shown to react with furan, 1,3 diphenyl benzofuran and cyclopentadiene.[11] Pyrrole is generally a poor diene in the Diels-Alder reaction, much less reactive than furan and only shows any significant reactivity when *N*-protected with an electron-withdrawing group. Figure 1 shows the three main protecting groups successfully used in pyrrole cycloaddition chemistry.



127 **135** **172**

Figure 1

Acetylene **287** is preferred over the two proven activated acetylenes **163** and **293** (Figure 2). The other active acetylenes would require much greater manipulation from their Diels-Alder adducts with pyrrole to arrive at 1,2 dihalo (or ditriflate) substrates, including the awkward removal of the activating ester and tosyl groups.

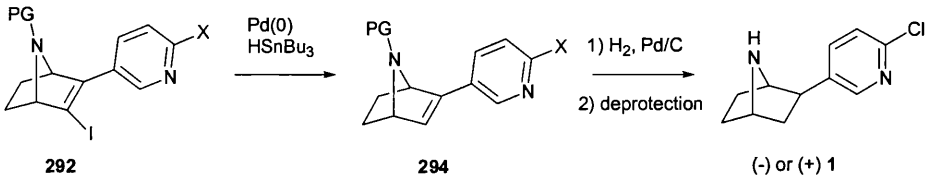


287 **163** **293**

Figure 2

The coupled product **292** should then be readily converted to the natural or unnatural enantiomer of epibatidine *via* three straightforward reaction steps (Scheme 2). Reduction of the remaining iodide, hydrogenation of the double bond and the cleavage of the amine protecting group (and possibly installing

the chlorine moiety if it proves sensitive to the reduction chemistry and the methoxy pyridine is required to this point).



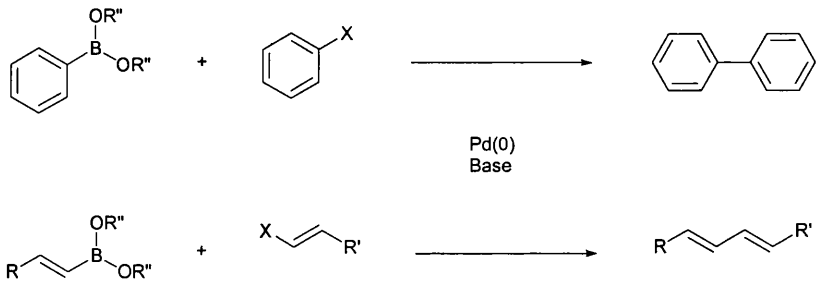
292 **294** (-) or (+) **1**

Scheme 2

This synthetic route, if successful, would be one of the shortest and most flexible as compared with those currently the literature. As both enantiomers and a range of different aryl analogues and their enantiomers could be prepared from the one intermediate, diiodide **290**.

The Suzuki-Miyaura cross coupling reaction

The Suzuki reaction is the cross coupling of an aryl, vinyl (or rarely alkyl) boronic acid (or ester) with an aryl or vinyl halide, in the presence of a palladium catalyst and base (Scheme 3). The were various forms of this coupling reaction reported from 1979 by the Suzuki group using different boronate species and vinyl and alkynyl,[13] allyl and benzyl,[14] and aryl[15] halides. However the first reaction using a boronic acid as the coupling partner, with aryl halides (iodides and bromides) was reported in 1981 by Suzuki and co-workers. [16]



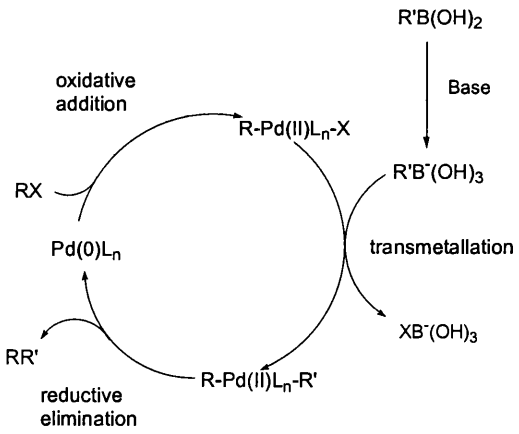
Scheme 3

The reaction is analogous to the other palladium catalysed cross-coupling reactions (Grignard, organolithium, organozinc) in terms of its mechanism and efficiency. But offers the significant advantages of air and moisture stability and tolerance of a much greater range of functionality than the organometallic cross-coupling partners. There are two excellent reviews on the scope and diversity of the Suzuki-Miyaura coupling and other organoboron reactions.[17, 18]

The closely related and very mild Stille reaction has the advantage that it does not require the presence of a base in the reaction, but utilises highly toxic organotin reagents as the coupling partners.[19] Aryl and vinyl boronic acids are by comparison relatively benign, non-toxic and easy to handle. The byproducts from Suzuki couplings are boronate salts and they can be readily separated from the coupled products usually by filtration. Another very useful aspect of Suzuki chemistry as opposed to Stille chemistry is the vast range of aryl, and heterocycle boronic acids that are commercially available, with new derivatives appearing regularly. These combined features have lead to the Suzuki reactions popularity in synthesis, as the cross-coupling reaction of choice.

The catalytic cycle for the Suzuki reaction is shown in Scheme 4. It is essentially the same mechanism as for all palladium catalysed cross-coupling reactions. The oxidative addition of the palladium across the carbon-halide (or triflate) bond is followed by a transmetallation step where the aryl or vinyl portion of the boronic acid is substituted for the halide or triflate. The base is required in the Suzuki-Miyaura reaction to promote the transmetallation step. The boron component is unreactive to transmetallation unless quaternised to its boronate complex. The rational for this is the increased nucleophilicity of the organic group when bound to the boronate as compared with the boronic acid.

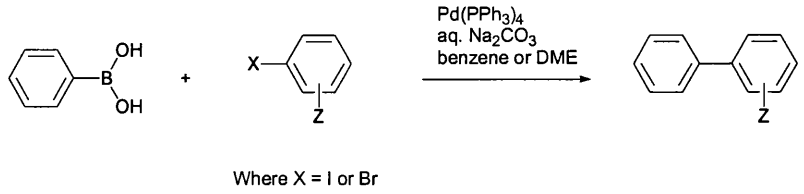
The catalytic cycle of the Suzuki-Miyaura coupling



Scheme 4

Finally reductive elimination of the two vinyl or aryl units completes the reaction and returns the palladium to its (0) oxidation state to begin another cycle.

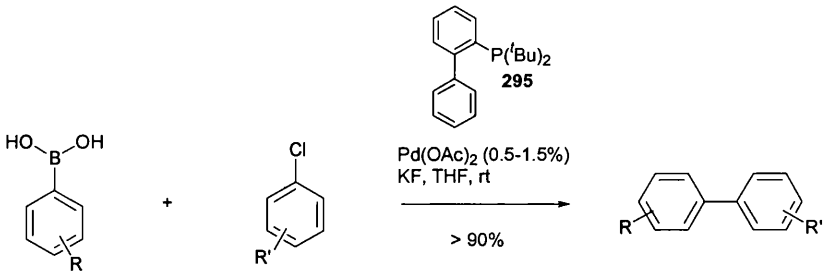
The original paper enabled the coupling of aryl bromides and iodides with phenyl boronic acid with tetrakis triphenylphosphine palladium in benzene[16] (adapted to use less toxic DME as the solvent[20, 21]) at reflux with Na_2CO_3 used as the base (Scheme 5). The DME conditions proved extremely general and can be applied to a wide range of different substrates.



Scheme 5

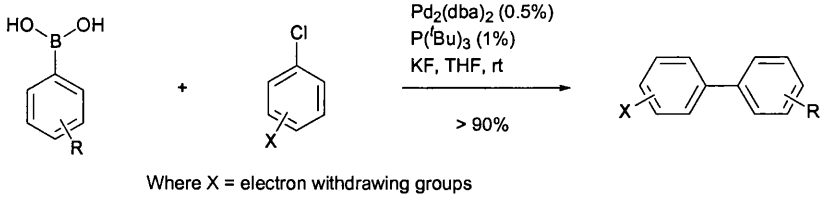
The methodology was expanded to enable the use of vinyl and aryl triflates as the electrophile component of the coupling reaction. Aryl chlorides were completely unreactive under the original conditions. This fact was suspected to be due to their relative reluctance to undergo oxidative addition. The development of the Suzuki-Miyaura coupling reaction has been such that that, with the development of more active palladium catalysts the coupling of aryl chlorides is now possible, even at room temperature.

In 1999 Buchwald *et al.* disclosed a catalytic system that would allow the coupling of aryl chlorides at room temperature with impressively low catalysts loadings using dialkyl biphenyl phosphines including di*t*butyl ligand **295** (Scheme 6).[22] The system was general and could be used for both activated (electron poor) aryl chlorides and deactivated (electron rich) aryl chlorides; excellent yields were obtained for both. A range of substituents could be tolerated on either of the aryl coupling partners in the *para* or *meta* positions without compromising the efficiency of the reaction.



Scheme 6

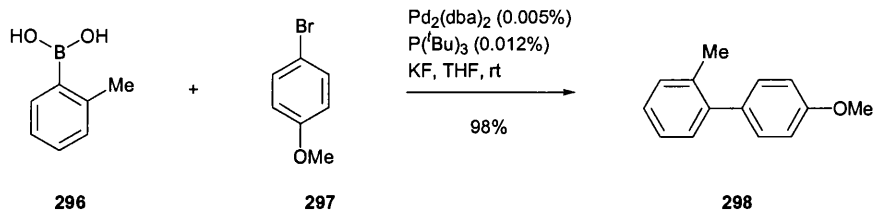
The group of Fu has also been active in the area of aryl chloride activation and their system is outlined below (Scheme 7).[23] With the tri*t*butyl phosphine ligand in a 1:1 ratio with palladium, activated aryl chlorides can be coupled with impressive yields with low catalyst loadings at room temperature. Heating was still required to couple unactivated aryl chlorides.



Scheme 7

Fu has also investigated lowering the catalyst loadings still further, to make this process attractive for industrial syntheses. With only 0.01% of palladium the coupling reaction of *o*-tolyl boronic acid **296** and *p*-

bromoanisole **297** was achieved in 98% yield (Scheme 8). This corresponds to an impressive turnover number of ~10,000.

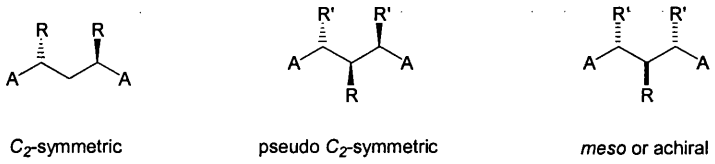


296 **297** **298**

Scheme 8

Desymmetrisation

A desymmetrisation reaction is one where a symmetrical substrate is transformed into a non-symmetrical product. For this to be a synthetically useful process it needs to be highly selective. There are three main classes of compounds that can undergo the desymmetrisation reaction, (Figure 3).



C_2-symmetric pseudo C_2-symmetric *meso* or achiral

Figure 3

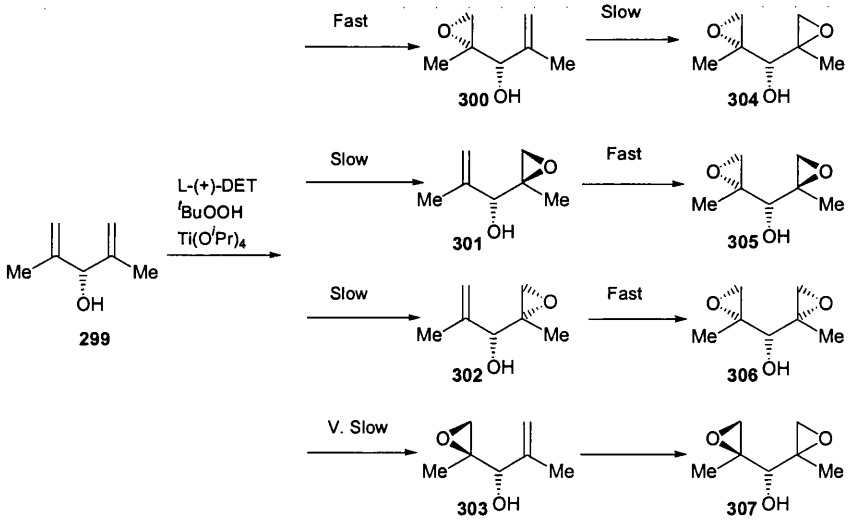
Of these, the simplest substrates are C_2-symmetric; the two groups A, are identical and reaction at either will give rise to the same product. These substrates are not of much interest as the only issue of control comes from minimising the *bis* reaction.

Pseudo C_2-symmetric substrates can be reacted selectively with diastereotopic group selectivity. This type of desymmetrisation is not very commonly studied due to the infrequent occurrence of suitable substrates, not through any inherent difficulty with the process itself.

The most interesting and widely used substrates are achiral or *meso* compounds. The two A groups are now enantiotopic and when reacted with enantiopure reagents or catalysts may yield enantioenriched products. Selectivity between the two groups can only be achieved with enantiopure reagents and is dependent on the interaction between catalyst (or reagent) and substrate. The reaction is useful because either enantiomer of product can be obtained from the same starting material by using the different enantiomers of the reagent or catalyst. Unlike a resolution, the yield of the desired enantiomer is not restricted to 50%; all of the achiral starting material can be converted to the required enantiomer of product. Another major advantage is that it allows reactions that have no inherent ability for

enantioselectivity, (for example ring closing metathesis, which only forms sp^2 hybridised carbon centres) to be carried out enantioselectively. Furthermore it has been shown that, even if the selectivity of the initial reaction is not complete the enantiomeric purity of the product can increase with reaction time due to an *in situ* kinetic resolution of the initial products that form. There is an excellent recent review on the current scope and diversity of catalytic asymmetric desymmetrisation strategies in the literature, by Willis.[24]

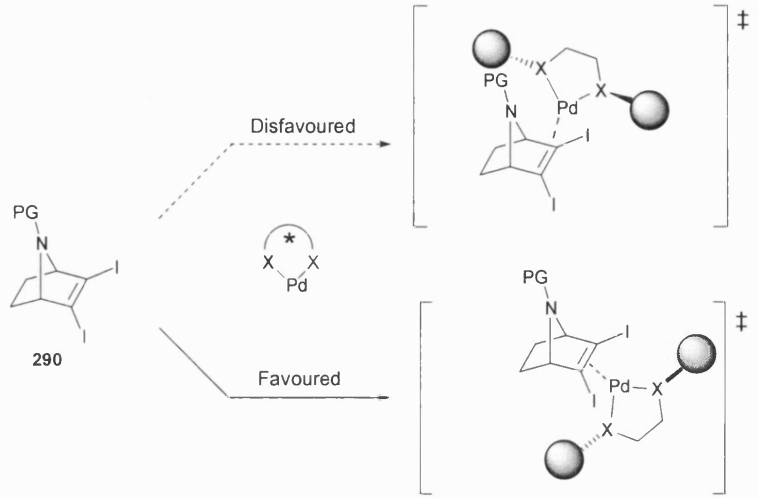
An excellent example of the benefits of this resolution was demonstrated by Schreiber *et al.* (Scheme 9).[25] This shows the desymmetrisation of divinyl alcohol **299** using the Sharpless asymmetric epoxidation protocol. The reaction of the diene **299** with the chiral Sharpless catalyst system can potentially give rise to four different stereo isomeric products **300, 301, 302** and **303**. The reaction rates are different for the formation of each isomer giving one major epoxide and two minor epoxides. The rate for **303** is so low that effectively it is not formed at all. The kinetic resolution takes place at this stage, as the two minor stereoisomers are rapidly converted to their *bis* epoxides, while the desired product reacts only slowly in the second epoxidation reaction. Thus as **301** is consumed the de of **300** increases and as **302** is consumed the ee of **300** increases. With sufficient reaction time **300** was obtained in >99% ee, > 99% de and an 85% yield.



Scheme 9

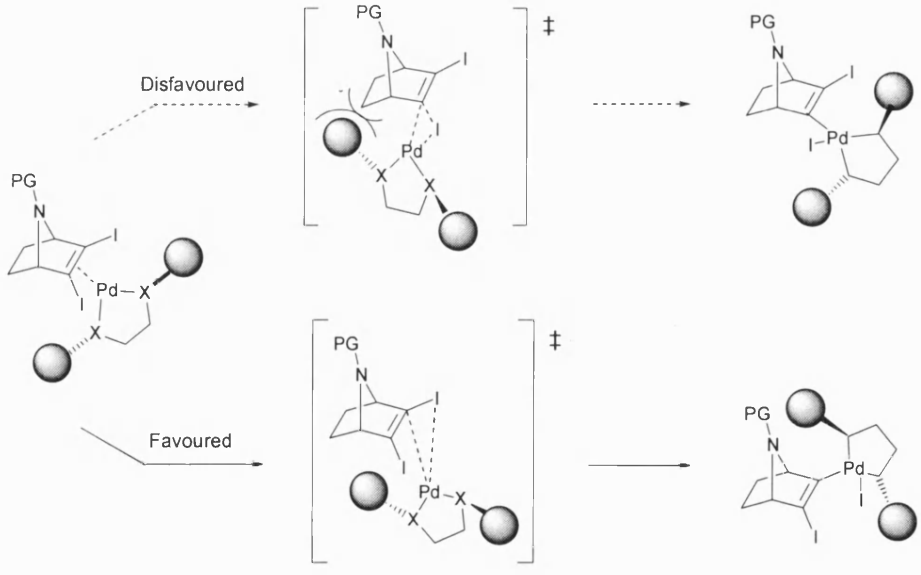
For the proposed desymmetrisation strategy to work in the synthesis of epibatidine, facial differentiation of the double bond of **290**, as in the epoxide example above, is extremely important. The control in the Sharpless epoxidation reaction comes from the directing effect of the hydroxyl group bound to the titanium catalyst. The proposed initial interaction between the catalyst and the substrate is the formation of a η^2-complex.[26] For this to form selectively on one face of the double bond requires there to be a significant steric difference between them as there is no directing effect to aid the coordination on one face or the other. It is assumed that the protected nitrogen would not be a potential electron donor to the metal due to the electron withdrawing protecting groups. Scheme 10 shows the two possibilities for the approach of an enantiopure pure palladium catalyst to substrate **290**. Assuming that the protecting group

on the nitrogen is reasonably large, approach from the top face should be unfavourable. This may well change, and be dependent on the protecting group. Leading to insertion of the metal into the carbon-iodine bond from the bottom face.



Scheme 10

This is likely to vary depending on the size of the protecting group, but is not important in this case as long as one face is favoured above the other (the double bond is restored at the completion of the reaction and therefore the direction of approach will not matter). Once the initial interaction between the metal and double bond has been achieved insertion should occur into the most sterically favoured carbon-iodine bond (Scheme 11).



Scheme 11

One of the enantiotopic iodines will be favoured over the other. Once the insertion has taken place the reaction should continue through the catalytic cycle and furnish enantio-enriched coupled product **292**. Approach from the opposite face by the same catalyst system should give rise to the alternate oxidative

insertion. Thus, even if the insertion process is 100% selective, if there is no facial discrimination by the catalyst a racemic product mixture will result.

Interestingly, the resulting enantiomer enriched by this process might change even with the same enantiopure ligand with a change in protecting groups present on the amine. This will be the case if the steric difference is enough to change favoured approach of the catalyst to the opposite face of the double bond.

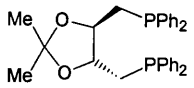
An *in situ* kinetic resolution, as in the epoxidation example, should aid the enantiomeric purity of the product. As any mono-product formed from the unfavoured insertion reaction should be much more reactive to further reaction than the desired product.

Enantioselective carbon-carbon bond forming reactions catalysed by palladium

The most common use of enantioselective palladium catalysis occurs in the Heck[27] and allylic substitution[28] reactions. They are both well studied and beyond the scope of this chapter. Of interest to the work proposed are the previous examples of enantioselective palladium cross-coupling reactions.

Enantioselective palladium catalysed cross coupling reactions

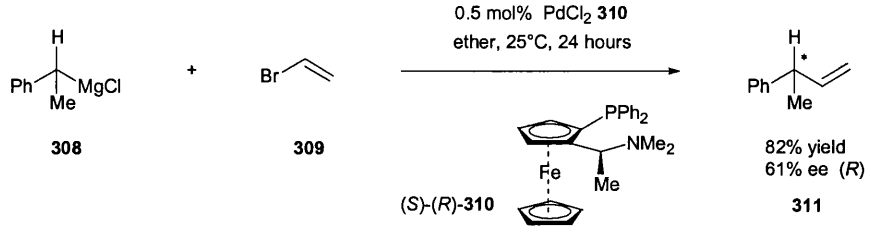
Enantioselective cross coupling reactions have been known since 1973 when Consiglio *et al.* demonstrated a Grignard coupling between a secondary alkyl Grignard **308** and vinyl bromide **309** using a nickel diphosphine catalyst system.[29] The reaction product was only obtained with low enantioselectivities, between 7 and 16% at best, utilising (-)-DIOP as the diphosphine ligand (Figure 4).



(-)-DIOP

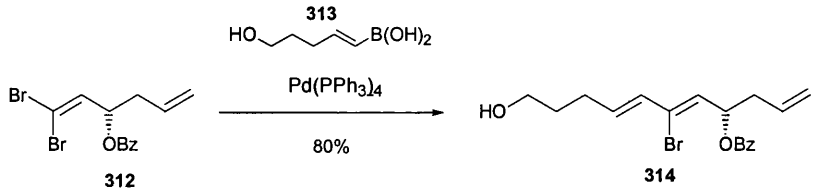
Figure 4

The same reaction was made much more efficient ten years later by Hayashi *et al.* through the use of a palladium ferrocenyl phosphine catalyst system (Scheme 12).[30] Through the use of ferrocene catalyst (*S*)-(*R*)-PPFA **310** the cross-coupled product **311** was obtained in a good yield and respectable 61% ee.



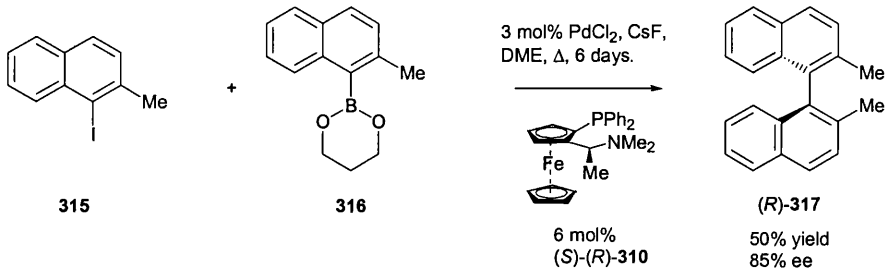
Scheme 12

Grignard reactions are the only cross couplings in the earlier enantioselective literature because (unlike the Stille and Suzuki reactions) secondary Grignard reagents form chiral centres directly during the reaction sequence. Despite this the Suzuki reaction was shown to be sensitive to steric environment as early as 1990 by Rousch *et al.* (Scheme 13).[31] The coupling of 1,1 dibromide **312** occurred selectively with boronic acid **313**. The *trans* addition product **314** was the only product that was isolated from this reaction.



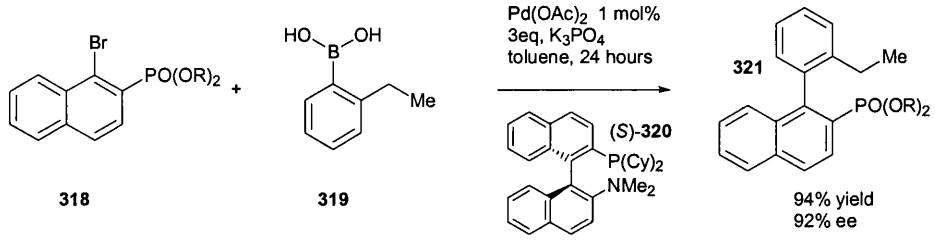
Scheme 13

It was not until very recently that the first non-desymmetrising enantioselective Suzuki couplings were disclosed in the literature. The first two being published, virtually simultaneously, were both involved in the preparation of axially chiral biaryl systems. Cammidge *et al.* synthesised binapthyl **317** with iodide **315** and boronic ester **316**. Their best result was obtained using (*S*)-(*R*)-PPFA **310** with CsF in DME at reflux for 6 days and achieving a good ee of 85% (Scheme 14).[32]



Scheme 14

Buchwald *et al.* were preparing biaryls of the type **321**.[33] Their results were impressive not only for the high yield and enantioselectivity exhibited in the products but the low catalyst loadings and room temperature reaction conditions. The best results obtained are shown in Scheme 15. This reaction is notable for the use of the novel monodentate dialkyl phosphine BINAP-like ligands (e.g. **320**) used in the catalyst system. These are the chiral equivalents of the biphenyl ligands used previously by this group to successfully couple aryl chlorides at room temperatures (Scheme 6).

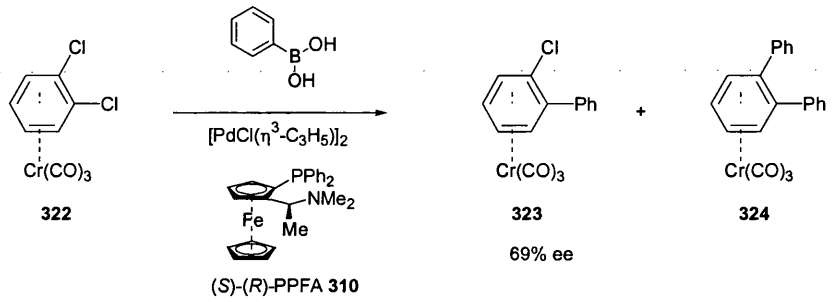


318 **319**

Scheme 15

Enantioselective desymmetrising palladium catalysed cross-coupling reactions.

The earliest example of a desymmetrising cross-coupling Suzuki reaction was the carried out by Hayashi and co-workers in 1994.[34] Planar *meso* chromium tricarbonyl compound **322** was screened in desymmetrising couplings with a variety of coupling partners (Grignard, organozinc, organostannanes and organoboronates) and ligands. Interestingly the best result was the reaction with phenyl boronic acid (Scheme 16), which provided the *mono* product in 69% ee also using the ferrocene ligand (*S*)-(*R*)-PPFA **310.**



322

(*S*)-(*R*)-PPFA **310**

323

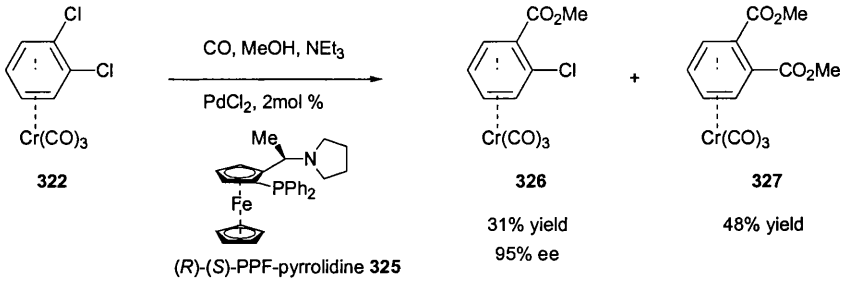
69% ee

324

Scheme 16

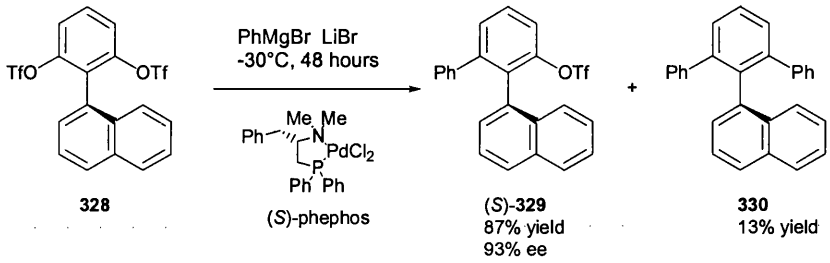
Intriguingly the use of organostannanes as cross coupling partners with *bis* chloride **322** resulted in the formation of only racemic products.

Further work on the same dichloride **322**, was disclosed in 2001 by Schmalz, in a palladium catalysed methoxycarbonylation reaction.[35] In this reaction significant kinetic resolution was found to occur with the ee obtained being directly proportional to reaction time and conversion of the starting dichloride **322**. With ferrocene ligand **325** and sufficient reaction time, *mono*-ester **326** was obtained in an excellent 95% ee (Scheme 17). The selectivity between the chlorides in the initial reaction was calculated to be 4:1. The rate of reaction of the second carbonylation however was calculated to be only 1.25 times that of the undesired reaction. Therefore the reaction had to be run for much longer (and thus lower yields of the *mono* chloride **326** obtained) to gain high enantiopurity.



Scheme 17

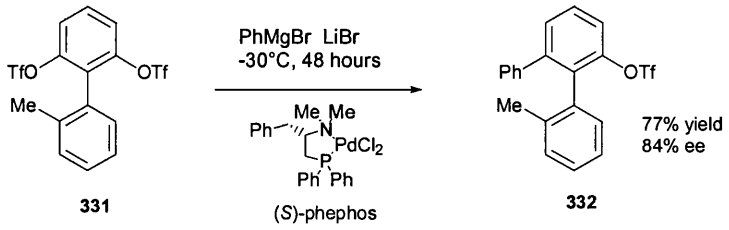
Hayashi *at al.* also disclosed a axial chiral desymmetrisation of *meso*-ditriflate **328** in 1995 (Scheme 18).[36] The transformation was achieved *via* a Grignard coupling using phenyl magnesium bromide and a $PdCl_2$(*S*)-phephos catalyst system. Impressive levels of yield and enantioselectivity were achieved with mono triflate **329** obtained in 87% yield and 93% ee.



Scheme 18

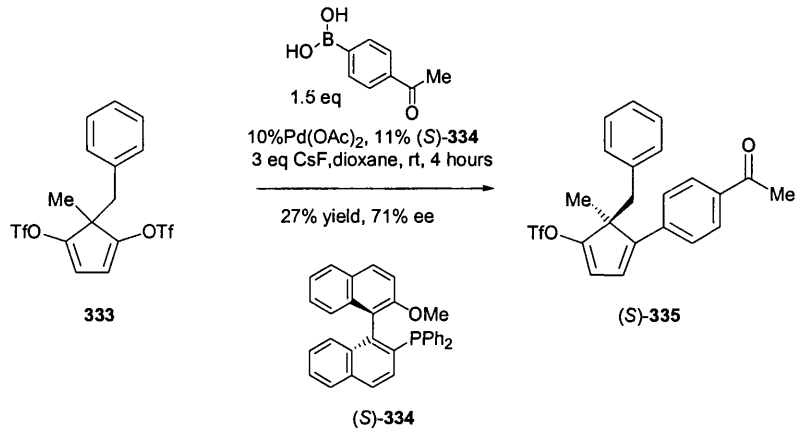
Hayashi *et al.* reported the enantioselectivity of the product improved with reaction time and with formation of the *bis* adduct **330**. This clearly demonstrated an *in situ* kinetic resolution was occurring and aiding product enantio-purity. Kinetic studies showed that the minor (*R*) isomer of **329** was consumed five times faster than the major isomer into the *bis* adduct **330**. This demonstrates the effect of improved selectivity has on the yield of the desired mono product. Schmalz required greater use of the kinetic resolution reaction due to poorer selectivity and the yield of the chloride **323** dropped to 31% to achieve 95% ee. While Hayashi obtained triflate **329** in 87% yield with a 93% ee.

The same reaction conditions were also applied to the much less sterically demanding *o*-tolyl analogue **331** that also gave the mono-phenylated product **332** in 84% ee (Scheme 19).



Scheme 19

Work within our own group has recently shown that ditriflate **333** can be desymmetrised with a high degree of selectivity under Suzuki reaction conditions using the mono phosphine ligand MeO-MOP, **334** (Scheme 20).[37] The synthesis of enantioenriched acetyl **335** was achieved in a 27% yield and a 71% enantioselectivity in four hours at room temperature. Ditriflate **33** was recovered in a 50% yield from the reaction mixture. Studies to increase the yield and selectivity of this process are ongoing. However it provides excellent precedent for the proposed study to provide an enantioselective synthesis of epibatidine.



333 (*S*)-**334** (*S*)-**335**

Scheme 20

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Results and Discussion

Part 1 - Preparation of *meso* substrates

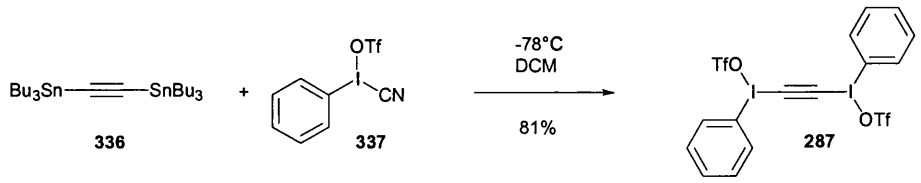
The use of hypervalent iodine chemistry

Preparation of bis[phenyl[[trifluoromethanesulphonyl]oxy]iodo]acetylene 287

***Via* the chemistry of Stang and Zhdankin**

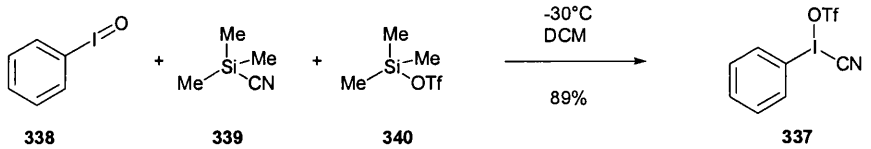
The synthetic effort towards epibatidine began with the preparation of the acetylene **287**, the dienophile required in the proposed Diels-Alder reaction to generate the desired substituted bicyclic adducts (Scheme 1, Chapter 2). The reaction partners, various protected pyrroles, are commercially available and so the focus of the initial synthetic efforts was into preparing **287** in sufficient quantities for Diels-Alder studies. Obviously this highly reactive *bis* iodonium species is not commercially available.

The acetylene was prepared as described in the literature (Scheme 1).[1] *Bis*(tributylstannyl)acetylene **336** was reacted with cyanoiodonium species **337** (Stangs reagent) in DCM at -78°C. The reaction required simply the addition of the two reagents at -78°C and on warming to 0°C the acetylene product precipitated out of solution and was filtered off.



Scheme 1

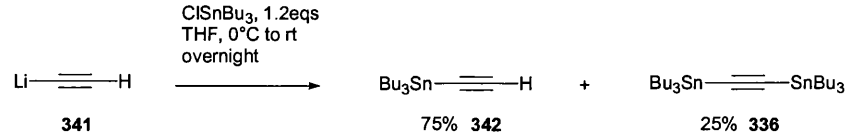
Stangs reagent **337** was prepared from iodosobenzene **338** in a single step (Scheme 2).[1] Iodosobenzene was treated with TMSCN and subsequently TMSOTf in DCM at -30°C. The reaction mixture was warmed to 0°C and the product was filtered off. Iodosobenzene was prepared from the commercially available iodosobenzene diacetate in one step.[2]



Scheme 2

Bis(tributylstannyl)acetylene **336** is commercially available but very expensive at £20 per gram. A literature preparation of tributylstannyl acetylene **342** was found, from lithiated acetylene, by Bottaro *et al.* in which the desired *bis* product **336** was formed as a by-product (Scheme 3).[3] Since the tributyltin

chloride was used in only slight excess and 25% of the product formed was the *bis* stannane **336**, it was assumed that it was this product that was actually favoured under these conditions. By increasing the amount of tributyltin chloride to 2.2 equivalents it was hoped the reaction could be driven to produce predominantly the *bis* product **336**.



Scheme 3

This was attempted (though the lithium acetylene used was purchased from Aldrich, stabilised with ethylene diamine **344** (Scheme 5) and not prepared from the reaction of BuLi with acetylene directly as dictated in their paper) and the initial result looked extremely promising. However, closer examination of the product obtained showed no quaternary carbon acetylene signals in the ^{13}C NMR spectra. The major product formed with the increase of tributyltin chloride turned out to be predominantly hexabutyl ditin **343** (Figure 1).

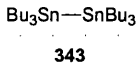
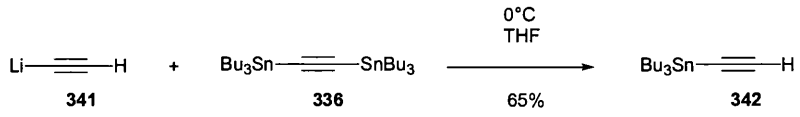


Figure 1

This result was repeated on several attempts with varying excesses of the tributyltin chloride used. In their paper, Bottaro *et al.* were not interested in *bis* product **336** and reported converting it to the desired *mono* stannane **342** by reacting it with more lithiated acetylene **341** in a disproportionation reaction (Scheme 4).[3]

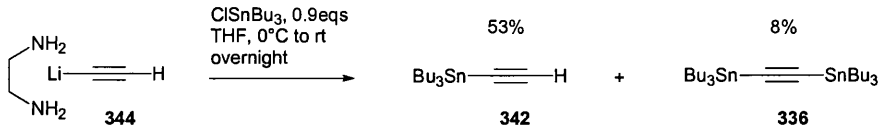


Scheme 4

It is entirely plausible that the hexabutyl ditin species **343** would undergo the same conversion to **342** when treated with lithiated acetylene, and that it was this species that was actually formed in their reaction, or at least a mixture of the two. ^1H NMR spectra of the two (**336** and **343**) are virtually superimposable and their boiling points are very similar. In our hands it was impossible to separate them *via* distillation.

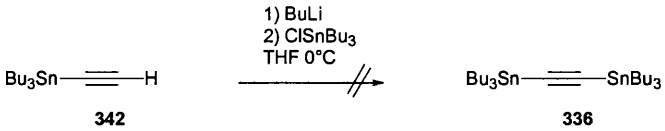
A stepwise reaction sequence was then envisaged. The best ratio of the reagents found for the reaction to prepare *mono* stannane **342** was a slight excess of the lithiated acetylene complex. These conditions produced none of the ditin **343** compound and a 53% yield of the mono adduct and an 8% yield of the *bis* stannane **336**. (Further searching of the literature during this work yielded a similar reaction published by

Stille and co-workers.[4] Their yield was lower, 31-35% of **342** and they also do not report the formation of the *bis* product **336**.) Purification of the two products was carried out *via* vacuum distillation.



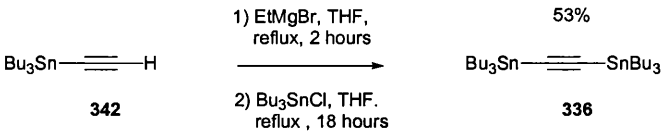
Scheme 5

Conversion of the *mono* stannyl acetylene **342** was first attempted *via* lithiation and quenching with tributylstannyl chloride (Scheme 6). This gave only trace amounts of **336** and returned ~80% of the starting material each time. Presumably transmetallation of the tributylstannyl group was competing with deprotonation of **342** and proving to be the favoured process.



Scheme 6

An investigation into the literature preparations of metal acetylenes revealed that lithiation was not a high yielding method for their synthesis. However the alternative Grignard conditions generally worked much more efficiently.[5, 6] A synthesis of **336** was then attempted using EtMgBr to generate the desired Grignard and quench it with tributyltin chloride (Scheme 7).[5]



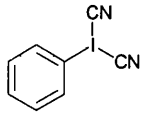
Scheme 7

This was successful with the preparation of *bis* stannane **336** in a 53% yield. With the chemistry to prepare the *bis* stannane elucidated, over 75 grams were prepared for the synthesis of the activated iodonium acetylene **287**.

The reaction to prepare Stangs reagent **337** (Scheme 2), was carried out as described in the literature. With the synthesis of this reagent completed and that of the acetylene **336**, the synthesis of the *bis* salt **287** could be attempted. The reaction appeared to proceed exactly as described in the literature with the product crystallising out of the reaction mixture (Scheme 1).[1] Unfortunately the product obtained, though in an identical yield to the one reported, was only about 80% pure as measured by ^{1}H NMR spectroscopy. The reaction was repeated many times with exactly the same result. The contamination appeared to be the same each time, a single compound, having the appearance of a substituted benzene ring by the pattern of signals in its ^{1}H NMR spectra. The contaminant was not unreacted Stang's reagent **337**.

Various attempts were made to prevent the formation of this product. Subtle changes to the ratio of the two reagents were tried as well as reducing the temperature. Excess Stangs reagent **337** caused the excess to appear in the product as well as the unknown contaminant. Excess stannane led to the formation of a non-crystalline sludge-like solid, presumably containing mono product. Reducing the maximum temperature to -20°C, or lower, resulted in no reaction. The reaction was also carried out using a commercial sample of the stannane **336** (purchased solely to use as a control) and gave the same yield of the same mixture of compounds. Recrystallisation was attempted but was limited by the stability of the acetylene. *Bis* iodonium acetylene **287** decomposes rapidly on contact with any solvent other than DCM and MeCN. Furthermore it is completely insoluble in DCM and decomposes in a few hours in MeCN at room temperature. No improvement in purity was ever witnessed after a recrystallisation attempt. (The acetylene cannot tolerate boiling MeCN; DCM was added to a solution of the acetylene in MeCN to cause precipitation.)

One of the co-authors of the paper, Dr Zhdankin, was contacted for advice, and claimed that the impurity was most likely *bis* cyano iodonium salt **345** (Figure 2).[7]



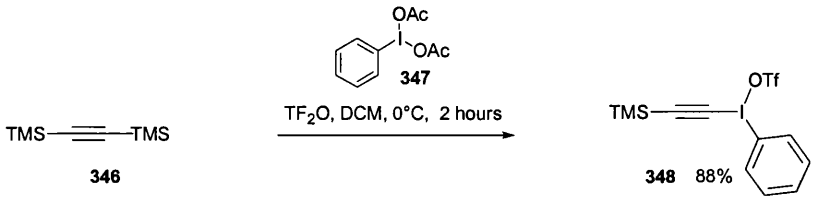
345

Figure 2

The impurity was being made in the formation of the Stangs reagent, according to Dr Zhdankin. The same impurity *was* seen in the ^{1}H NMR spectra of this material, although very much weaker. The Stangs reagent being used was already >96% pure. (No attempt to purify this material further had been made due to fears over its sensitivity.) However he provided alternative conditions that would reduce the formation of this species still further. This involved using a slight excess of TMSOTf and an increased reaction time. This was carried out as Zhdankin indicated and proved successful. The Stang's reagent **337** obtained was much cleaner than before but in a lower yield. However the treatment of this purer material with the stannane **336** still yielded exactly the same product mix as before. This proved that the impurity was being formed in the reaction and was not a previous impurity simply being concentrated under the reaction conditions.

Alternative conditions to form *bis* iodonium acetylene 287

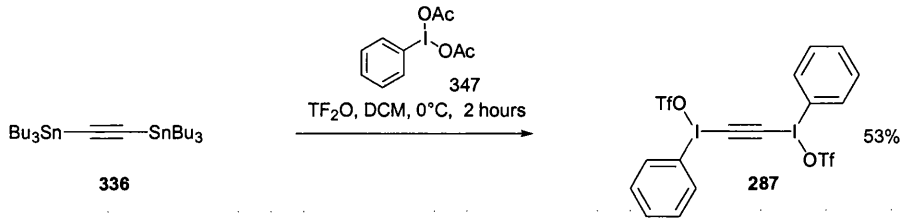
Whilst working on this problem a paper was published by Kitamura *et al.* that described the formation of mono phenyl iodonium acetylene salts from the much more benign *bis*(trimethylsilyl)acetylene **346** (Scheme 8).[8] Their procedure was simpler; the acetylene salts **348** were prepared from the reaction of commercially availably diacetate **347** and triflic anhydride directly with acetylene **346**.



Scheme 8

The reaction was readily repeatable and consistently high yielding. Attempts were made to modify their procedure to synthesise **287** directly from *bis* silyl acetylene **346** in one step. Unfortunately the reaction only yielded mono products or tar, if forcing conditions were employed.

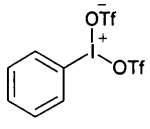
The *bis* stannane **336** was then treated with the alternative conditions described by Kitamura *et al.* in an attempt to prepare acetylene **287** (Scheme 9).



Scheme 9

The reaction was successful if somewhat low yielding in comparison with the Stang chemistry. However the product was identical to that prepared by the previous methods, it contained the same impurity in a virtually identical ratio. This result was unexpected and very frustrating. The presence of the same impurity ruled out completely Dr Zhdankin's theory about the *bis* cyanoiodonium species **345** as it would be impossible to form this during the reaction under the Kitamura conditions. Also at this time NMR data was obtained for *bis* cyanide **345**, which showed that it could not be the impurity. Along with this data, it was found that **345** is soluble in DCM, which would have meant it would have been washed out at the end of the reaction.[9]

The other possible candidate had been the *bis* triflate impurity **349** (Figure 3). However the use of excess TMSOTf in the reaction to gain purer Stang's reagent **337** suggested that this candidate was unlikely. However, ^{1}H NMR data was sought from the literature to verify this from a Russian journal. Unfortunately the ^{1}H NMR data quoted in the paper was found to have been obtained on a 60 MHz spectrometer and the aromatic protons were all quoted as one five proton broad multiplet.[10]



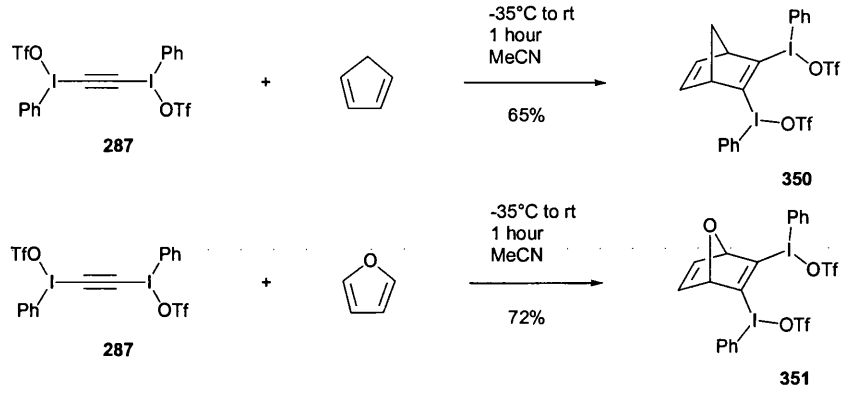
349

Figure 3

All further attempts to purify the material were abandoned and crude **287** was tried in reactions with suitable dienes.

Diels-Alder chemistry of acetylene **287**

Crude acetylene **287** was treated with 2 equivalents of cyclopentadiene and furan to test its reactivity in the Diels-Alder reaction. Both reactions were performed as dictated in the literature and the yields obtained were equivalent, allowing for the 80% purity of the starting material (Scheme 10).[1] Pleasingly the products **350** and **351** were obtained in almost 100% purity (as judged by their ^{1}H NMR spectra). The impurity present in the acetylene was either destroyed during reaction or washed out of the reaction mixture on completion in the workup.



Scheme 10

The reaction was then attempted with a range of other dienes (Figure 4), to obtain the adducts and to judge the reactivity of the acetylene with diene compounds other than cyclopentadiene and furan.

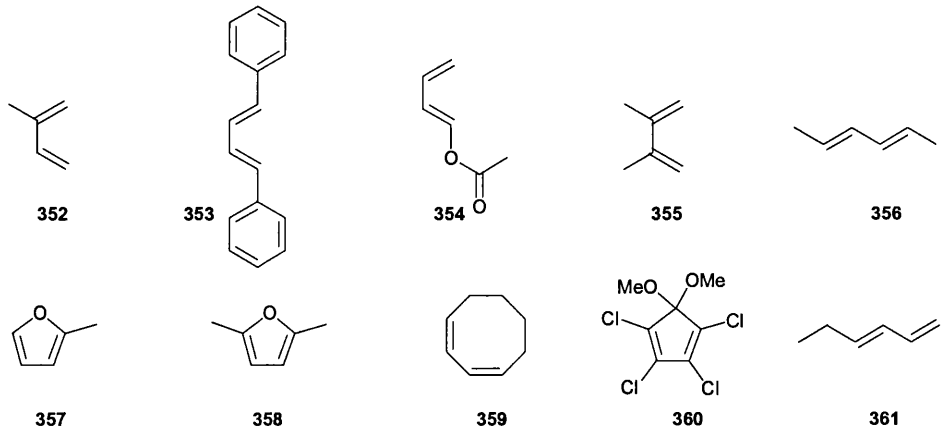


Figure 4

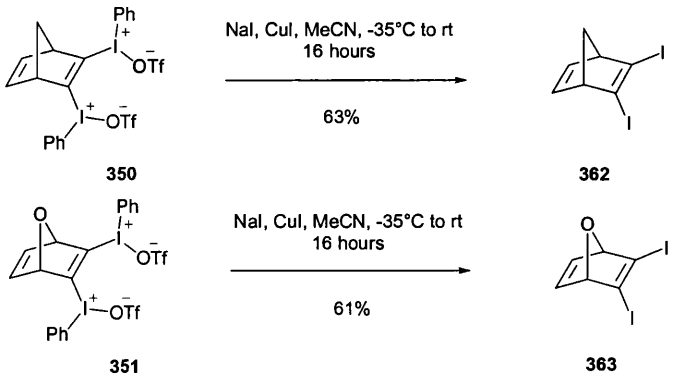
Unfortunately no products from Diels-Alder reactions were obtained with any of the dienes shown. Those that were simple hydrocarbon based caused no obvious problems on addition but failed to yield any useful products. Heteroatom containing dienes such as **354**, **357**, **358** and **360** caused the reaction mixture

to blacken rapidly with their addition or as they warmed to room temperature, resulting only in the formation of black tar. These results were obviously frustrating considering the efforts put into making the acetylene. This was disappointing also for the fact that they were all expected to be more reactive dienes than pyrrole.

The Diels-Alder reaction was attempted with BOC-pyrrole **135** anyway to confirm the unsuitability of the *bis* iodonium acetylene substrate **287** as a dieneophile. The addition of the pyrrole caused the reaction mixture to go black faster than any of the previously attempted dienes. This unfortunate result was repeated several times. All plans to use this method to prepare the necessary 2,3 dihalo-aza bicyclo[2.2.1]heptene substrates were then abandoned.

The attempted cleavage of the iodonium salts

The reaction was still able to provide salts of the furan and cyclopentadiene adducts. If cleaved to form the halides these products would still be potentially very useful model substrates for the desymmetrisation of 1,2 dihalo aza bicyclo alkenes. Taking the salts **350** and **351** and treating them with NaI and CuI as demonstrated in the literature led to the formation of the products **362** and **363** respectively (Scheme 11).[11]



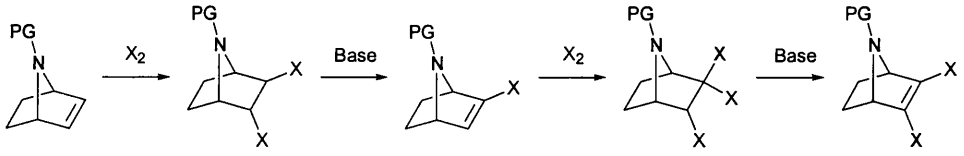
Scheme 11

The yields given are based on the crude product mixture on the ratio of signals between the desired products and the by-product iodobenzene produced in the reaction, in the ^{1}H NMR spectra. The literature method for purification involved blowing nitrogen over the crude oil to evaporate the more volatile iodobenzene. This was followed but always was accompanied by considerable decomposition of the desired products. Solid material would form, as the crude product mixture was concentrated. A number of methods were attempted to try and prevent this but none were successful. Alternative conditions were tried that involved the use of soft nucleophiles that purportedly cleaved the Ph-I bond of the salt, thus preventing the formation of the troublesome iodobenzene.[11] However, none of the nucleophiles that were tried resulted in the formation of the desired products.

The decision was made that the iodonium chemistry was not going to produce the compounds desired and it was ceased. Its (at times) unpleasant and awkward nature was not worth pursuing if the nitrogen system was definitely beyond reach and the carbon and oxygen analogs were proving extremely difficult to obtain and purify.

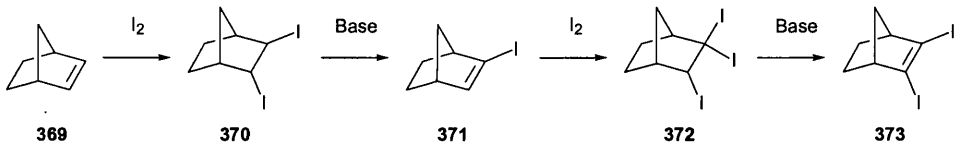
Preparation of meso-dihalides *via* addition elimination strategy

The use of the activated acetylene **287** as a viable starting material for the substrates required for the synthesis of epibatidine (and model substrates to demonstrate the Suzuki desymmetrisation methodology) was ruled out. A much simpler and less exotic method to construct these alkenes was sought. The simplest methodology that was envisaged was an addition/elimination sequence of halogen to the alkene compound **364** (Scheme 12).



Scheme 12

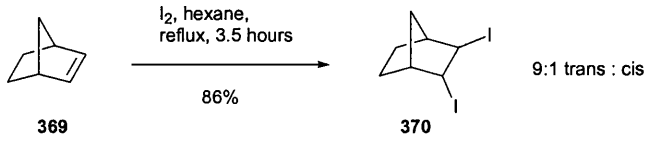
While simple in concept this method has the disadvantage that it adds a further four steps to prepare the vinyl dihalide species **368**, from alkene **364** which is not readily available in itself. Considering the synthetic work needed just to prepare **364** it was decided to test this chemistry on the commercially available norbornene **369** and synthesise the model substrate, diiodide **373** (Scheme 13). Iodine rather than bromine was chosen for this sequence as in palladium coupling chemistry, iodine is generally much more reactive to oxidative addition. For successful enantioselective reactions, lower temperatures are favoured and thus high reactivity of the substrates is desirable. Therefore the iodine compound was favoured for study.



Scheme 13

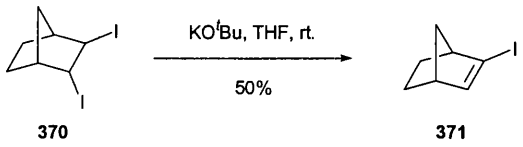
Attempted preparation of 2,3 diiodonorbornene **373** *via addition-elimination strategy*

The preparation of diiodide **370** from norbornene was taken directly from the literature (Scheme 13).[12] The diiodide **370** was obtained in a 9:1 mixture of *trans* and *cis* products that are separable *via* chromatography.



Scheme 14

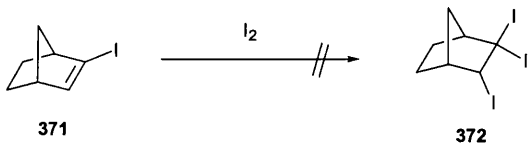
However, separation of the two isomers is unnecessary as it was found that they undergo basic dehydroiodination with equal efficiency to form the vinyl iodide **371**. While not a novel compound the vinyl iodide **371** had not been prepared *via* this method.[13] The best conditions obtained for the transformation are shown in Scheme 15.



Scheme 15

The transformation occurred cleanly and almost instantaneously upon addition of the base but only a 50% yield of the product was obtained. Attempts to improve this by reducing the temperature of the reaction were unsuccessful. Adding the base at -78°C or at 0°C and allowing the reaction mixture to warm to room temperature provided no improvement in the yield. No further modifications were attempted, as a 50% yield was suitable for our purposes.

Unfortunately no conditions could be found for the formation of triiodide **372** from the vinyl iodide **371** (Scheme 16).



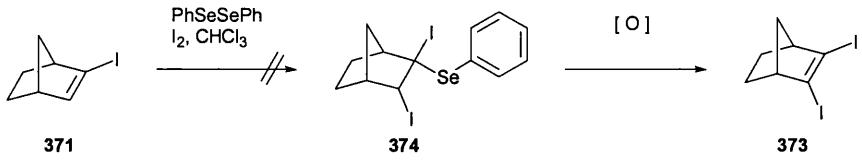
Scheme 16

Further direct iodination of **371** proved impossible. The reaction was tried in a variety of solvents and temperatures. In the majority of cases the starting material was recovered. Sealed tube reactions were tried at elevated temperatures in both polar and non-polar solvents. These reactions either returned the starting material or produced break down products. The steric bulk of three iodine atoms in such close proximity appeared to be too great an energy barrier to overcome.

The use of phenylselenium iodide

We turned our attention to selenium chemistry in an attempt to circumvent this problem. It was hoped that the alkene **371** would react with an equivalent of phenylselenium iodide to yield addition product

374. This would then be cleaved by oxidation and subsequent elimination to form the diiodide **373** (Scheme 17).

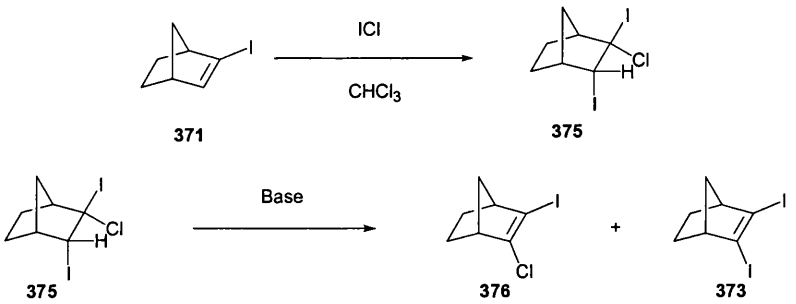


Scheme 17

Unfortunately despite the consumption of the starting material, the product **374** was never isolated. The non-polar nature of the compounds made separation of the crude material very difficult. Treatment of the crude reaction product with oxidation conditions never lead to the formation of the vinyl diiodide **373**.

The use of iodine monochloride

The addition of ICl to the vinyl iodide would result in the formation of a trihalide product. It was first hoped that if product obtained was **375** with the two iodine atoms *trans* position to each other then a selective, kinetic controlled, elimination of HCl might be possible, (despite the fact that iodine is thermodynamically the better leaving group leading to elimination of hydrogen iodide as the favoured process) as the usual favoured geometry for an E_2 elimination has the two groups anti-periplanar to each other (Scheme 18).

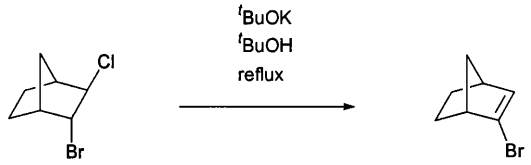


Scheme 18

However, an investigation of the literature showed that in the case of substituted norbornanes, the elimination reaction has been extensively studied and it has been shown that the *exo-cis* reaction pathway predominates.[14, 15] This has been explained by the fact that the geometry of the groups on norbornane are such that they cannot attain the 180° dihedral angle, the geometry preferred under bimolecular elimination conditions. Instead the second allowed angle of 0°, *syn* or *cis* elimination becomes the favoured process.

In the case of norbornene the *exo-cis* predominates over the alternative *endo-cis* pathway, it is argued, largely for purely steric reasons. This mechanism is favoured kinetically to the extent that it has been shown to override the normal thermodynamic leaving group priorities, (Br > Cl) in chlorobromide **377**, (Scheme 19). The *trans-exo*-chloride **377** was the only one of the four isomers studied (*cis-exo*, *cis-endo*,

trans-endo-chloride) to eliminate HCl under treatment with base. The other three gave almost exclusively the vinyl chloride product on treatment with the same reaction conditions.

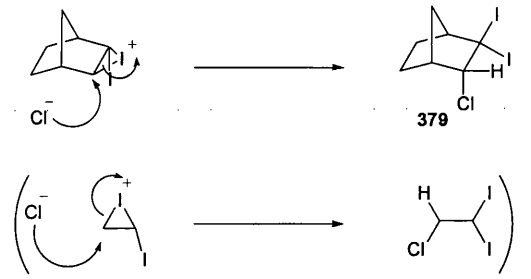


377 **378**

99% purity

Scheme 19

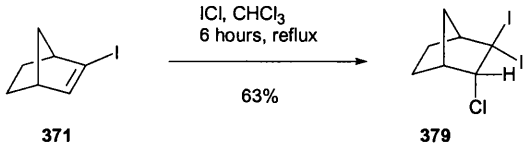
Considering the mechanism for the addition of iodine monochloride, assuming the formation of an iodonium ion intermediate shows that it is more likely that the geminal iodide species **379** will be formed (Scheme 20). The approach of the chloride will be most favoured from the hydrogen side of the former double bond.



Scheme 20

This compound would be the worst-case scenario as far as the elimination chemistry is concerned as either mechanism of elimination, *trans* or *exo-cis* would result in the formation of the undesired chlorodiiodide **376** (Scheme 18).

The reaction was carried out as shown in Scheme 21 with the addition of ICl to a stirring solution of the vinyl iodide in $CHCl_3$ followed by a 6 hour reflux. The reaction yielded one main product, which was elucidated to be the undesired geminal iodide **379** by its ^{13}C NMR spectra.



371 **379**

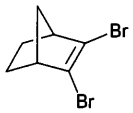
Scheme 21

The only quaternary carbon was too high field to be bonded to a chlorine atom. The lowest field carbon was a CH carbon and was assigned as the C(Cl)-H carbon. This reaction proved very hard to repeat, ICl is very sensitive and the first sample had gone off before the reaction was tried again. The next two

commercially obtained samples had decomposed before they were opened and a 1M solution in DCM seemed to cause the breakdown of the starting material. No attempts were made to treat the small quantity of trihalide **379** obtained with base to obtain the eliminated product. All further work on the iodination chemistry of norbornene was abandoned. Focus turned to the preparation of the bromine analogue.

The synthesis of 2,3 dibromonorbornene 380

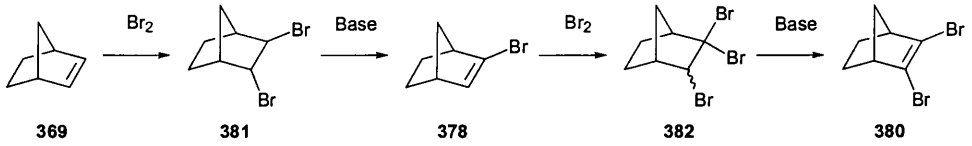
This dibromide compound **380** was the least favoured of the two possible norbornene dihalide derived substrates, due to the reduced reactivity of bromines over that of iodides in the Suzuki-Miyaura reaction (Figure 5).



380

Figure 5

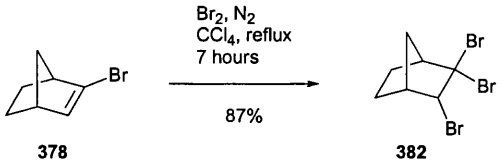
The dibromide **380** was a literature compound and had been prepared from norbornene in the same addition/elimination sequence as was attempted for the iodine analogue (Scheme 22).[16]



369 **381** **378** **382** **380**

Scheme 22

The reason this was not attempted earlier (in addition to the reactivity in the Suzuki reaction) was that the step to generate tribromide **382** from vinyl bromide **378** looked awkward. The conditions for the transformation involved the addition of bromine vapour carried in nitrogen, into a solution of the vinyl bromide in carbon tetrachloride at reflux, over 7 hours.[16]



378 **382**

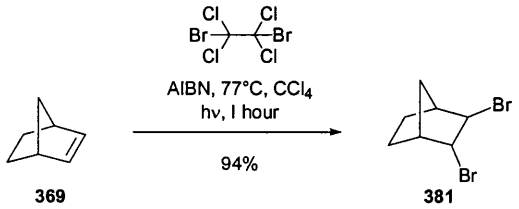
7:3 mixure of endo : exo

Scheme 23

This suggested that the reaction was difficult to perform if these were the optimised conditions and work concentrated on the iodine analogue. However, with the failure of the iodine chemistry, vinyl dibromide **380** became the main target.

The bromination of norbornene *via* standard (ionic) conditions (Br_2, DCM -78°C or Br_2, CCl_4 0°C) results in the formation of many different *mono* and *bis* brominated products being routinely produced.[17, 18] The norbornene skeleton undergoes a series of cationic rearrangements on the formation of the bromonium ion intermediate.

To obtain clean bromination of the double bond only, it was found that radical brominating conditions were needed. The protocol of Fry *et al.* was followed where norbornene was warmed to 77°C in carbon tetrachloride with 1,2 dibromotetrachloroethane and AIBN and treated with white light (Scheme 24).[19]

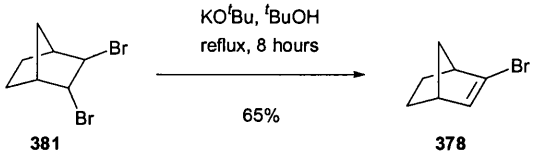


369 **381**

Scheme 24

This provides the brominated product **381** cleanly in an excellent 94% yield. The original conditions state the use of a 2000W sun lamp, but it was found that a 60W desk lamp worked just as efficiently. This reaction could be scaled up readily, to yield the dibromide **381** in 20-30 gram batches if required.

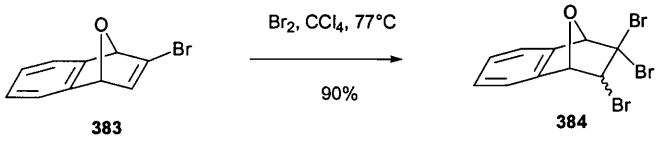
The conversion of the dibromide into vinyl bromide **378** was achieved using a slightly modified procedure described by Kwart and Kaplan (Scheme 25).[17] The dibromide **381** was dissolved in ^{t}BuOH and treated with KO^{t}Bu at reflux for 8 hours. The eliminated product is obtained in a 65% yield. (The modification comes from the use of commercial butoxide. In the paper Kwart *et al.* prepared theirs *in situ* with the addition of potassium metal to the ^{t}BuOH.)



381 **378**

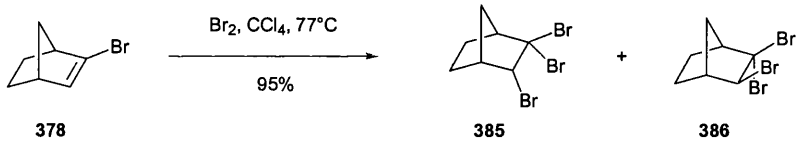
Scheme 25

For the preparation of the tribromide a recent method described in a publication for radical bromination of vinyl bromides to form tribromides was applied. The substrates used in the paper were oxabicycles, analogous in structure to ours. Rather than adding gaseous bromine *via* a stream of nitrogen, Altundas *et al.* brominated bicycle **383** by adding a hot solution of bromine in carbon tetrachloride to a solution of the alkene in CCl_4 at 77°C (Scheme 26).[20] The reaction cleanly provided the mixture of desired tribromides **384** in excellent yield after a five-minute stir once the dropwise addition of the bromine was complete.



Scheme 26

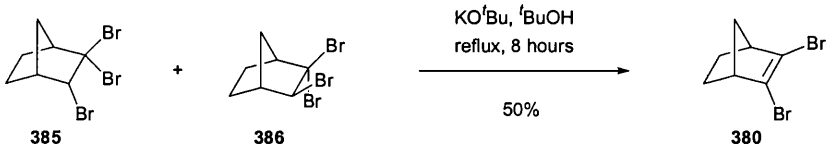
This methodology seemed much simpler to perform than the literature method to brominate vinyl bromide **378** and was tested first (Scheme 27). The procedure proved highly successful and the mixture of tribromides **385** and **386** was isolated in a 95% yield. A great improvement over the literature preparation.



Scheme 27

The two isomers were obtained in the same 3:7 ratio (as determined by ^{1}H NMR spectra of the crude product) exactly as reported in the literature under the more awkward radical conditions of Gassman and Gennick.[16] The original paper also reported that it was not possible to separate the two compounds. Therefore no attempts were made to separate them and the mixture was used crude in the next step.

The dehydrobromination of **385** and **386** was carried out exactly as dictated in the literature (Scheme 28).[16] The crude mixture of tribromides **385** and **386** were dissolved in ^{t}BuOH and treated with KO^{t}Bu at reflux for 8 hours. The vinyl dibromide **380** was obtained in a 50% yield as a colourless oil after purification *via* vacuum distillation.



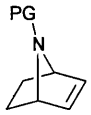
Scheme 28

Once the dibromide product was confirmed the reaction sequence was repeated from norbornene on a larger scale, and 10-12 gram batches of dibromide **380** could be readily prepared.

Preparation of nitrogen analogues

For this chemistry to be used in a synthesis of epibatidine the nitrogen analogue of the dibromide **380** needed to be prepared. The chemistry from the norbornene **369** to 2,3 dibromo norbornene **380** has been demonstrated to be straightforward and simple. To apply this chemistry to the epibatidine ring system the aza analogue of norbornene is required as the starting point. This nitrogen equivalent to norbornene

364 (with differing protecting group functionality) is not commercially available and has to be prepared (Figure 6).

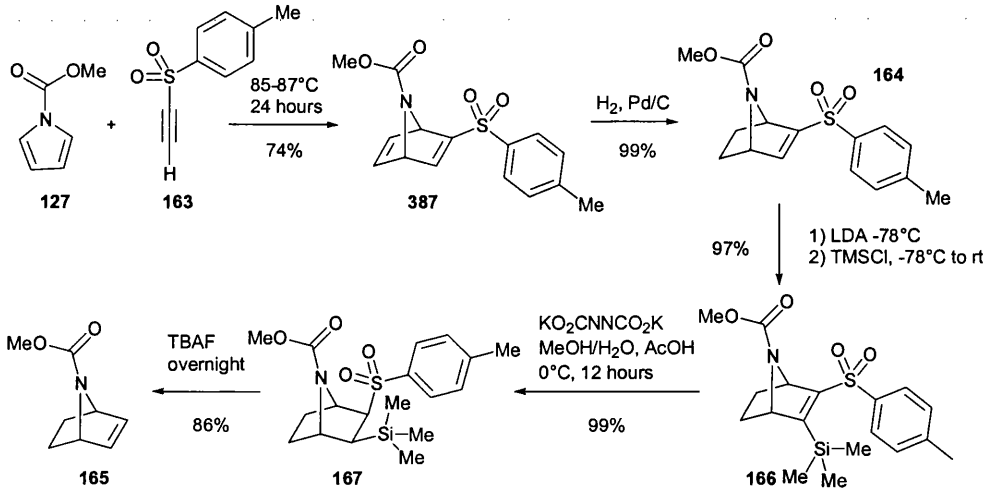


364

Figure 6

The preparation of BOC alkene ***171***

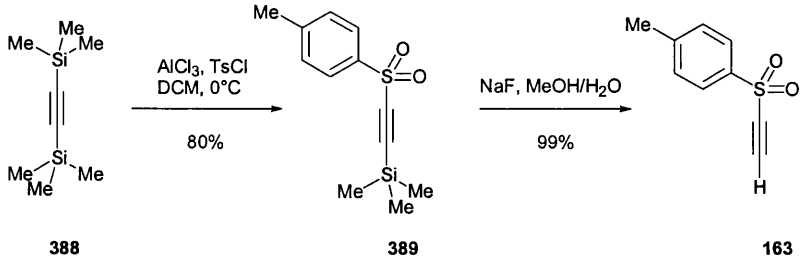
The most efficient route in the literature to an aza norbornene analogue was the preparation of the methyl carbamate protected derivative **165** (Scheme 29).[21] This chemistry was published by Kaufmann and co-workers and provides the alkene in a very respectable yield. The usual Na/Hg amalgam reduction of the sulphone **164** was avoided due to its low yields and poor reproducibility by a β-elimination strategy. Saturated silyl-sulphone **167** (prepared from **164** in two steps) was treated with TBAF to prepare alkene **165** in good yield.



Scheme 29

The methyl carbamate protected pyrrole **127** used in the synthesis is commercially available but expensive. The BOC protected analogue **135** was chosen instead for its reduced price per gram and also because it is much more readily cleaved than the methyl analogue.

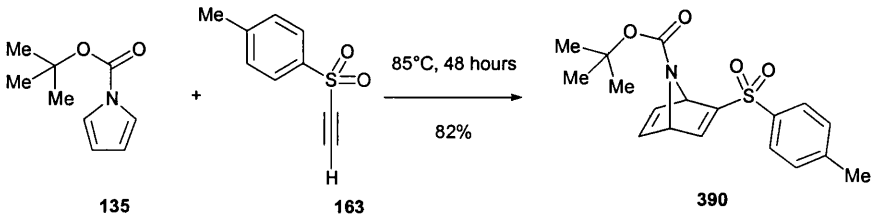
Tosyl acetylene **163** is also commercially available but is extremely expensive, costing fifty pounds per gram. It is readily synthesised however, in two straightforward steps in the literature from *bis*(trimethylsilyl)acetylene (Scheme 30).[21, 22]



388 **389** **163**

Scheme 30

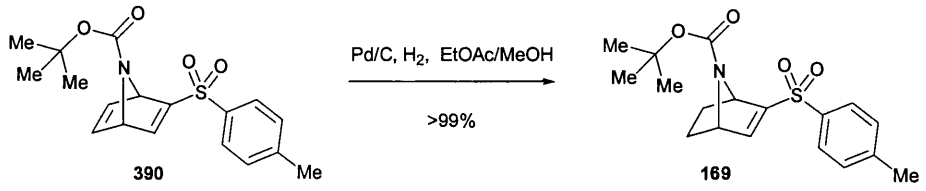
For the reaction of BOC pyrrole **135** with tosyl acetylene **163** a more efficient procedure was found in the literature than the Kaufmann procedure. The conditions of Leung-Toung *et al.* were used (Scheme 31).[23] Two equivalents of freshly distilled pyrrole **135** were stirred with acetylene **163** at 85°C for 48 hours to yield diene **390** in 82% yield.



135 **163** **390**

Scheme 31

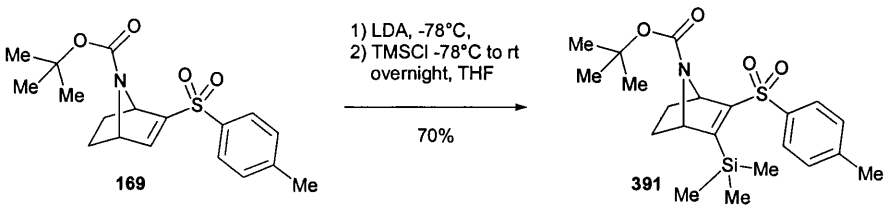
The unsubstituted double bond in **390** was then reduced using Pd/C and a hydrogen atmosphere in either EtOAc or methanol, as Kaufmann reported, to yield vinyl sulphone **169** in virtually quantitative yield (Scheme 32).[21] The consumption of hydrogen was not closely monitored as was stated in the literature. Vinyl sulphone **169** was found to be extremely resistant to further reaction and the reaction could be left for many hours after completion of the desired reaction with insignificant loss in yield.



390 **169**

Scheme 32

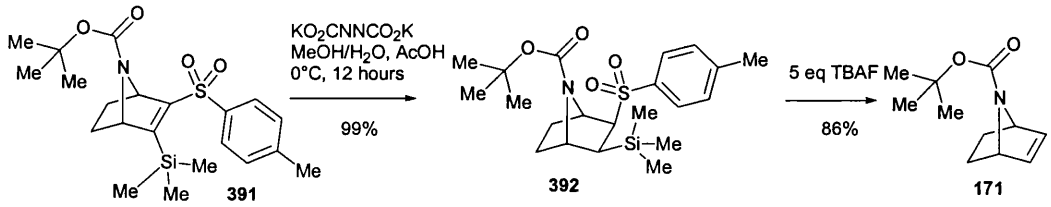
Cleavage of the sulphone by the Kaufmann method proved more difficult. Initially only about 40% efficient, the reaction of vinyl sulphone **169** with LDA and then quenching with TMSCl never yielded more than 70% of the desired addition product **391** after many attempts at optimisation (Scheme 33).



Scheme 33

A significant amount of the material appeared to be breaking down under the reaction conditions. The identity of these products, which could be isolated as a mixture *via* chromatography was never elucidated despite considerable effort.

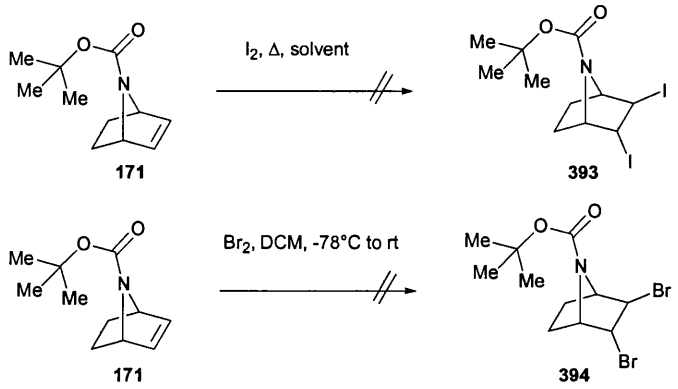
Pleasingly, the conversion of silyl **391** to the alkene **171** proceeded smoothly *via* the Kaufmann diimide reduction and TBAF induced cleavage protocols giving identical yields to those quoted in the literature for the methyl carbamate analogue (Scheme 34). The diimide reduction of the double bond was selective and virtually quantitative in yield. (Dipotassium azodicarboxylate was freshly prepared before the reaction according to the preparation reported by Groves *et al.*)[24] The fluoride-induced degradation of **392** was carried out with five equivalents of a one molar solution of TBAF in THF overnight. Purification was *via* alumina filtration in the literature (for alkene **165**) although the BOC alkene product **171** was stable to silica gel flash chromatography.[21]



Scheme 34

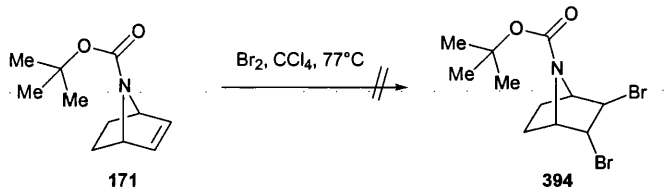
*Conversion of BOC alkene **171** into halogenated material*

The halogen addition reactions of alkene **171** proved difficult. Iodination under conditions used to prepare 2,3 diiodo norbornane (Scheme 35) proved ineffective, with starting material being returned unreacted. Different solvents were tried but no reaction was seen. Bromination, with bromine in DCM at -78°C proved destructive, only breakdown products could be obtained from this reaction.



Scheme 35

The radical conditions that were so successfully employed on vinyl bromide **378** were tried (Scheme 36). The reaction was followed by TLC and showed loss of starting material and formation of new products. However on workup, the reaction mixture decomposed rapidly on concentration *in vacuo* from a colourless solution to a black residue within a few seconds. Careful washing of the reaction mixture with sodium carbonate and sodium thiosulphate solutions failed to prevent this decomposition.

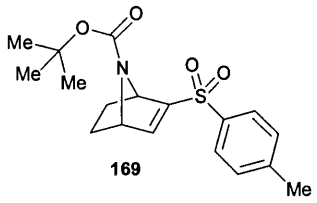


Scheme 36

Unforeseen formation of tritosyl dimer 396

It was thought that the difficulties experienced trying to brominate alkene **171** could be due to the BOC group. The acid lability of this group had been a concern from the beginning. It was decided that alternative protection should be tried. The tosylate group was the favoured replacement for the BOC protecting group. The sulphonamide group being extremely resistant to acid and basic conditions which would be required for the addition/elimination sequence needed to install the dihalide functionality from the bare alkene. The usual difficulty in using tosylate functionality as an amine protecting group is its cleavage. This usually requires harsh reducing conditions such as a Na/Hg amalgam. There is literature precedent for the removal of a tosyl group from the amine in an epibatidine synthesis (Scheme 43, Chapter 1) in good yield, so this was not a great concern for us.

It was decided to try to exchange the protecting groups early in the synthetic sequence to the alkene **171** and not on the alkene itself. The decision was made to change the protecting groups on the vinyl sulphone **169** (Figure 7).

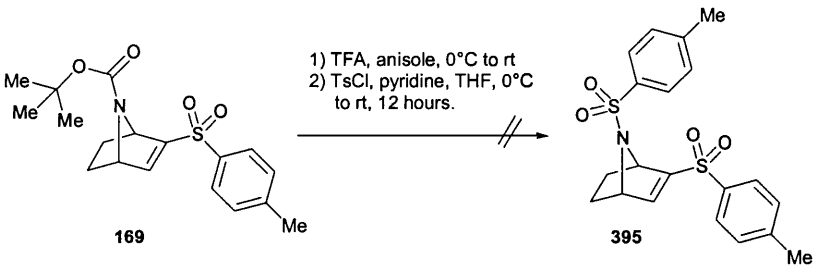


169

Figure 7

The reasons were two-fold, one because of the quantity of alkene **171** remaining (and its value) and two, the desire to see if the troublesome TMS addition step under LDA conditions (a step in the synthesis of **171**) would be more efficient with a more robust protecting group. The additional products obtained in the reaction could never be fully identified but appeared to have a reduced ratio of the strong *t*butyl signal) in their spectra. It was felt that somehow some of the compound was deprotecting under these conditions. With the sulphonamide group present the chances for deprotection affecting the outcome of the reaction would be greatly reduced.

Vinyl sulphone **169** was treated, first with TFA and then excess pyridine and two equivalents of tosyl chloride (Scheme 37). The main product obtained from this reaction was not the one that was expected. The expected *bis* tosyl product **395** was not synthesised at all.

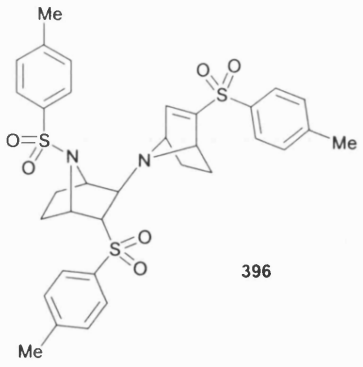


169 **395**

Scheme 37

The reaction was not clean and produced several products, although there was one main product that corresponded to the majority of the material. After thorough purification the main product was isolated and appeared to contain three different tosyl groups by ^{1}H NMR spectroscopy. The mass spectroscopy result showed several peaks but none that enabled a structure determination.

The material once purified was a colourless, highly crystalline solid and a single crystal was prepared for X-ray analysis to help identify the product obtained. The result when obtained was surprising, the compound had performed a conjugate addition on another molecule of itself to form dimer **396** (Figure 8). The X-ray crystal structure is shown in Figure 9. The hydrogen atoms are omitted for the sake of clarity.



396

Figure 8

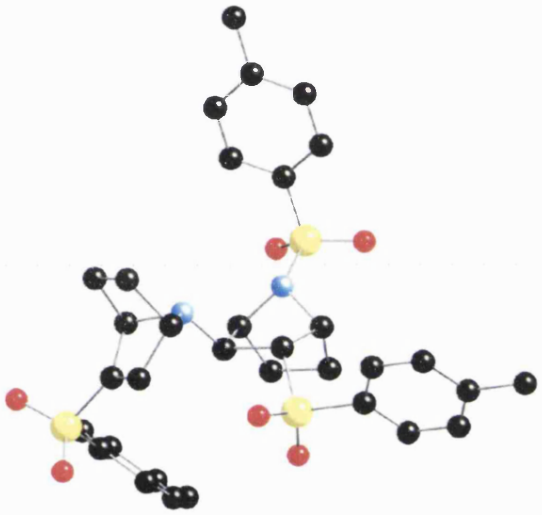
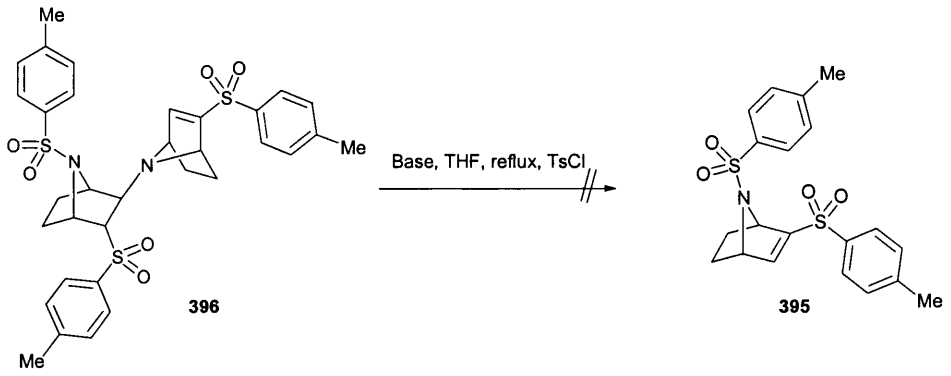


Figure 9 – dimer 396

Presumably once the basic conditions had liberated the free amine, this performed a conjugate addition on the double bond of a neighbouring molecule. The second reaction (to form a trimer) must have been sterically unfavoured, the remaining free amine was too hindered to do a second addition once the 1st conjugate addition had been completed. Thus the competing tosylation reaction then became favoured to form the tritosyl compound **396**. The minor products that were not fully identified are presumably the other addition isomer and possibly some trimerised adducts.

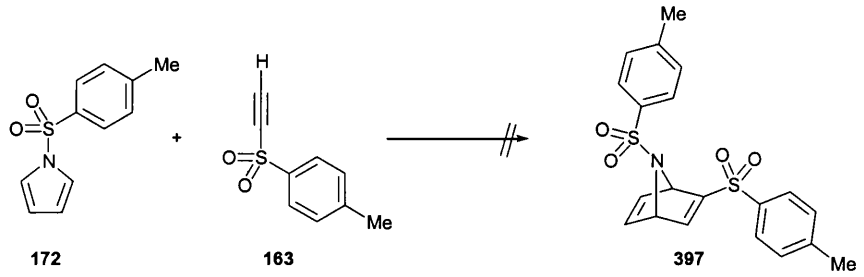
Attempts were made to reverse the addition reaction by treatment of the dimer **396** with base under dilute conditions with an excess of TsCl to trap out the desired *bis* tosylate **395** (Scheme 38). The reaction was tried with NEt_3, DBU and KO^tBu at room temperature and then at reflux in THF. The reactions never yielded any useful products. Extended reaction times increased the number and amounts of breakdown products. Starting material **396** could be isolated unreacted from these experiments.



Scheme 38

The dimer **396** was also treated with BuLi and then TsCl in a last attempt to try and cleave the dimerised product into the *bis* tosyl adduct but as in the previous cases, no useful products were obtained.

Since *bis* tosylate **395** was still an interesting compound and that the protecting group exchange had failed to provided it, a direct method of preparation from tosyl pyrrole was examined. However attempts to prepare *bis* tosylate **397** (and then **395** after hydrogenation) from the Diels-Alder of tosyl pyrrole **172** with tosyl acetylene **163** (under the same reaction conditions that Trudell had used to react BOC pyrrole **135,** toluene 90°C, 24hrs), resulted in no reaction (Scheme 39).[23, 25] Both starting materials could be recovered.



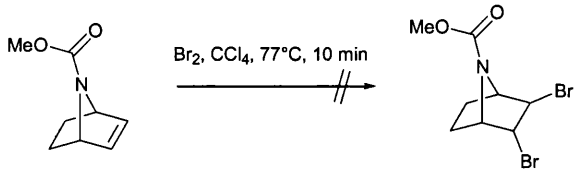
Scheme 39

Preparation of the methyl carbamate alkene **165**

With this difficulty experienced in exchanging protecting groups and while the identity of **396** and the reason for its formation was being determined, the Kaufmann synthetic sequence was repeated, this time using the methyl carbamate-protecting group (Scheme 29). (Protected pyrrole **127** was synthesised according to the procedure of Wang and Anderson.)[26] The LDA and TMSCl addition reaction was just as difficult as had been experienced with the BOC protected material. Similarly, more polar products were obtained and the yield of silane **166** obtained was only 60%. The rest of the deprotection steps were achieved as reported however and a small amount of alkene **165** was produced for further study.

Attempted preparation of dibromide 398

With alkene **165** in hand, attempts were made to brominate the double bond. Similarly to its BOC protected analogue, alkene **165** decomposed under standard low temperature ionic bromination conditions. The high temperature radical conditions used so successfully on norbornene-2-bromide were carried out and the TLC of the reaction mixture showed complete conversion of the starting material (Scheme 40).[20] Wary of the same fate as the BOC compound, the reaction mixture was washed thoroughly with a 10% thiosulphate solution as well as a saturated bicarbonate solution before drying over sodium sulphate. However rapid decomposition of **398** occurred as the solvent was removed *in vacuo* as had occured with the BOC analogue **394**. This was a major disappointment. It appeared that the dibromide compounds were generally not stable although no rational explanation for this behaviour could be found.

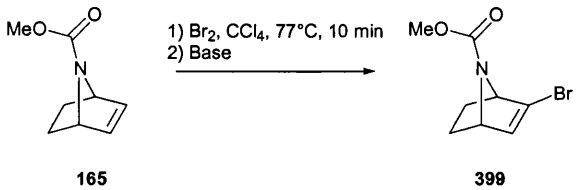


165 **398**

Scheme 40

The use of phenylselenium bromide to prepare vinyl bromide 399

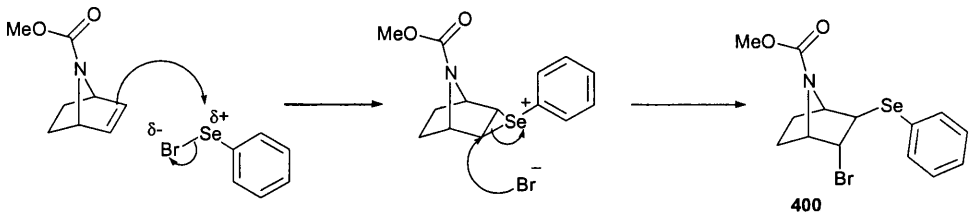
We speculated that a solution to the problem might be to try and prepare the vinyl bromide **399** directly and bypass the dibromide **398** compound completely. There were two methods considered to attempt this. The first that was proposed was to repeat the radical brominating chemistry and then treat the crude dibromide **398** with base *in situ*, to generate vinyl bromide **399** in the hope that this would be stable enough to survive concentration and purification (Scheme 41).



165 **399**

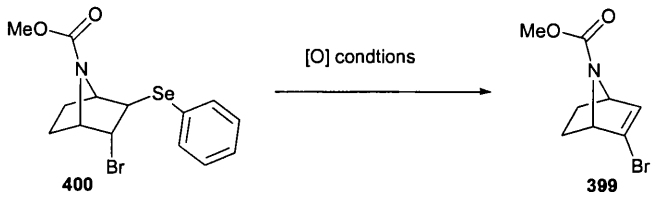
Scheme 41

The second method proposed was the reaction of phenyl selenium bromide with alkene **165**. This reacts in the same mechanism as any electrophilic addition to a double bond to provide intermediate addition product **400** (Scheme 42).



Scheme 42

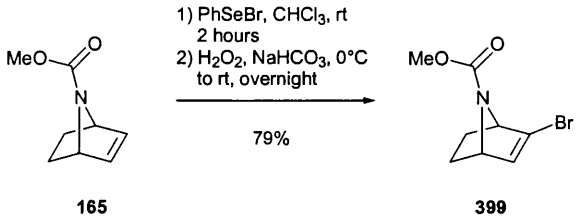
Selenoxides are unstable and β-eliminate to regenerate the alkene. So from the addition product, mild oxidation conditions, usually peroxide based, oxidise the selenide and spontaneous elimination of the oxide occurs to yield the alkene (Scheme 43). For a recent and useful review of selenium chemistry within organic synthesis, see Wirth.[27]



Scheme 43

Selenides are highly toxic compounds but the handling of them is usually minimised by performing these two reactions in one-pot. In this way the selenium species are never isolated or purified.

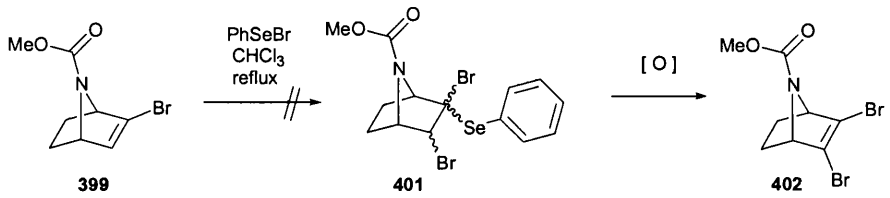
The latter method was attempted first. This reaction sequence was carried out on substrate **165** using slightly modified conditions of Arjona *et al.* (Scheme 44).[28] The reaction was extremely clean and gave solely vinyl bromide **399** in a 79% yield.



Scheme 44

Attempted synthesis of dibromide **402** *via phenylselenium bromide*

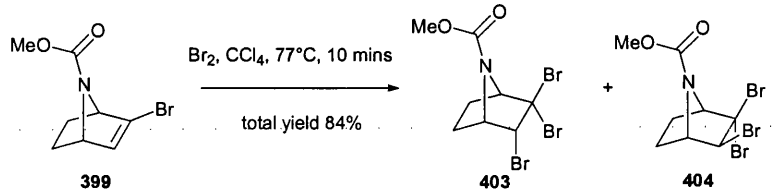
The reaction was so simple to perform and work-up that initially it was hoped the reaction could be repeated on the vinyl bromide **399** to yield the dibromide **402** in one pot (Scheme 45). However the addition of phenylselenium bromide to the vinyl bromide **399** was not achieved even in $CHCl_3$ at reflux. The reaction was also repeated in toluene to increase the reaction temperature still further but only breakdown products were obtained.



Scheme 45

The preparation of tribromides **403** *and* **404**

With the failure of the second addition of PhSeBr, alternative conditions were sought to brominate vinyl bromide **399**. Radical bromination (again using conditions of Altundas *et al.*),[20] proved successful with tribromides **403** and **404** being prepared in 56% and 28% yields respectively (Scheme 46). The two isomeric tribromides were readily separated *via* flash chromatography.



Scheme 46

From the ^1H NMR spectra of the products, it was suspected that the least polar isomer was tribromide **403** the *endo* isomer, due the coupling seen between one of the bridgehead carbons to the C(Br)-H proton. The more polar adduct showed no coupling between the bridgehead proton and the C(Br)-H proton and was assumed to be the *exo*-bromide isomer. A good synopses of the highly diagnostic coupling constants in azabicyclo[2.2.1]heptanes can be found in the excellent review by Chen and Trudell.[29]

The more polar isomer tribromide **404** formed a crystalline solid on standing. The less polar compound was much slower to solidify. A single crystal, grown from the more polar adduct **404** in DCM confirmed (by X-ray analysis) the assignment of the stereochemistry based on ^1H NMR analysis was correct. The more polar adduct, was the *exo*-bromide isomer **404** (Figures 10 and 11). A curious feature of this structure is the difference in angle of the *exo*-bromines. Clearly the bromines are sterically influencing each other and are adopting a distorted conformation to minimise the unfavourable interaction.

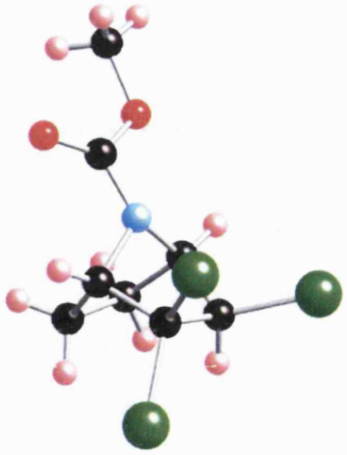


Figure 10 – tribromide 404

As can be seen from the view down the carbon-carbon bond, this distortion is not limited to the bromines themselves but affects the whole bicyclic structure (Figure 11). The whole ring system seems to be adopting a puckered conformation. This is very graphic evidence for why the attempts to prepare norbornane triiodide analogue met with failure. The bicyclic structure appears to have to adopt a fairly strained conformation to accommodate three bromines. The internal bond angles of the ring at the bridgehead carbons (CH_2-C_{brid}-CBr (or Br_2)) are 106.6° and 111.6°. Iodine is larger than bromine (Atomic radii: Br = 114pm, I = 133pm; van der Waals radii: Br = 182 pm, I = 198 pm)[30] and therefore presumably the bicyclic structure cannot distort enough to accommodate three iodine atoms. The offset angle of the two *exo* bromine atoms is 22.3° when viewed down the carbon-carbon bond (Figure 11). The angle between the geminal bromides is surprisingly only 107.5°, less even than the natural tetrahedral angle of 109°. Though this is no-doubt restricted by the strained bicycle structure C_{brid}-C(Br_2)-C(Br) angle = 100°). The distance between the geminal bromines is 314 pm and the distance between the two *exo* bromines is 331 pm. Clearly these distances are significantly less than the combined van der Waals radii of two bromine atoms (364 pm) and confirm the reason for the distorted conformation of the molecule.

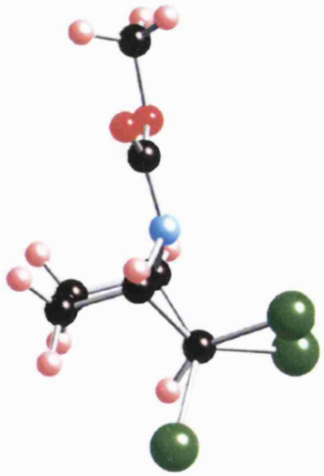
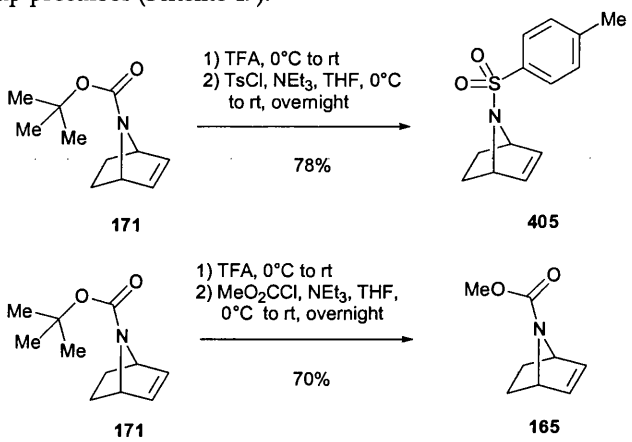


Figure 11 – tribromide 404

The amount of material left at this stage was low and it was not considered worth attempting to optimise elimination conditions to the dibromide **402** until more material could be brought forward.

Synthesis of protecting group analogues, alkenes 165 and 405, from BOC alkene 171

Considering the effort in bringing the two carbamate alkene isomers **165** and **171** through the synthetic sequence separately, it was hoped that a single compound could be made that could be converted to the other protecting group analogues at the alkene stage. The BOC compound was the most likely candidate due to its ease of cleavage. The tosyl compound was ruled out due to its un-reactivity in the Diels-Alder chemistry and the harsh conditions to needed to cleave a sulphonamide group. With the alkene free of the sulphone, there should be no problem of conjugate addition. The BOC alkene **171** was investigated to see if it could be deprotected and reprotected as the methyl carbamate **165** and tosyl protecting group **405** analogues. The reactions were carried out under the same conditions, TFA followed by base and the relevant protecting group precursor (Scheme 47).



Scheme 47

Both the compounds could be prepared *via* the BOC compound. The tosylate compound was prepared in a good yield of 78%; the methyl carbamate was only slightly less efficient and was formed in 70% yield. This was an encouraging result as the early synthesis could concentrate on the production of the single BOC alkene **171** and all the other compounds can be made from this one.

The tosylate alkene **405** was highly crystalline and single crystal X-ray analysis was obtained (Figure 12) that showed that the aromatic rings preferred geometry was nearly parallel to the double bond. This suggested there is potentially some π–interaction between the two unsaturated systems. Although the position could also be dependent on the unfavourable steric interaction of the *exo* protons and the tosyl ring when compared with the planar alkene system.

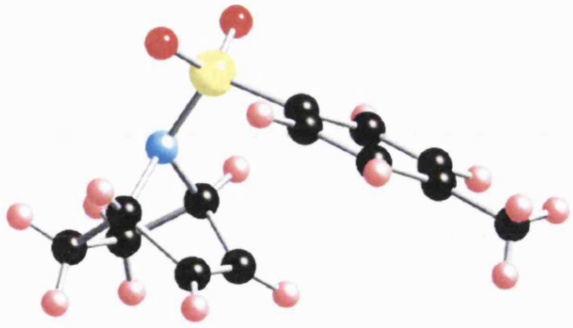


Figure 12 – alkene 405

Considering the importance of the protecting group in our desymmetrising strategy is was considered worth investigating the possibility of π-stacking when using the tosylate protecting group. From the literature it was found that the interatomic distance between the two π-systems was required to be between 300 and 400 pm for an interaction to occur.[31, 32] The groups need also be planar (or perpendicular) to each other for the π-clouds to positively interact with each other. As can be seen from the view from side on the aromatic ring is aligned nearly perfectly with the plane of the double bond (Figure 13). From the data it was possible to ascertain the distances between the carbon atoms of the double bond and the front three atoms of the tosyl aromatic ring. The average distance between these atoms is 331 pm (largest gap 358 pm and the smallest 319 pm) and this puts the gap at exactly the distance predicted by the literature for such an interaction. Further evidence would have to be gleaned from ^{1}H NMR spectra comparisons with tosyl compounds that definitely do not π-interact. At this time, however this was the first tosyl protected amine bicycle we had prepared and comparisons were not possible.

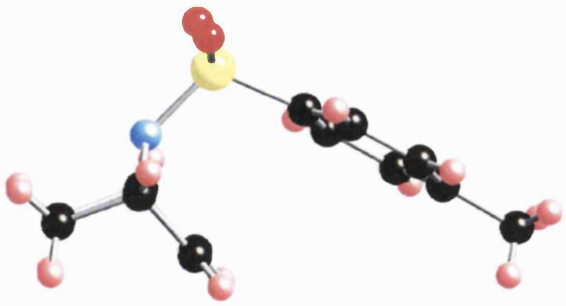


Figure 13 – alkene 405

Interestingly the plane of the aromatic ring is not aligned exactly with the rest of the structure. Neither is the direction of the aromatic ring straight in relation to the rest of the molecule (Figure 14). This seemed unusual considering the symmetry in the rest of the molecule but is most likely the result of a crystal packing effect.

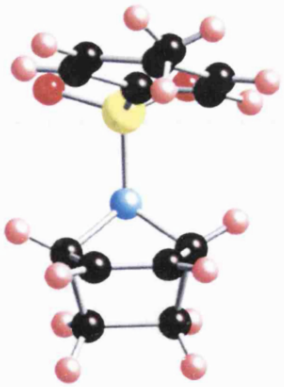
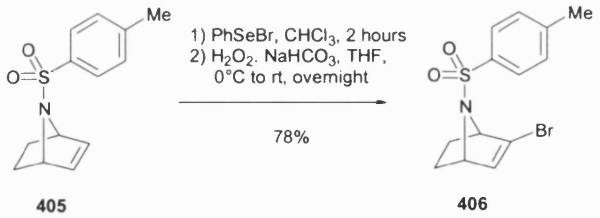


Figure 14 - alkene 405

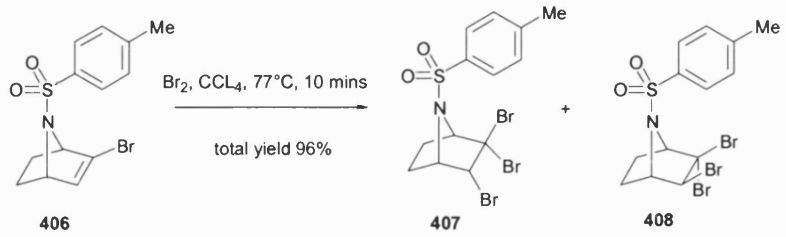
The preparation of tosyl dibromide **409**

With the alkene **405** prepared, it was hoped to repeat the chemistry tested on the methyl carbamate analogue and go one stage further and prepare the first vinyl dibromide. The tosylated alkene **405** was then reacted with phenyl selenium bromide in identical conditions to those tried with the carbamate alkene **165**. (Due to the success of this process, none of the other methods for bromination were tried on this substrate.) This reaction was equally successful on this substrate and provided the vinyl bromide **406** in a good 78% yield over the two-step sequence (Scheme 48).



Scheme 48

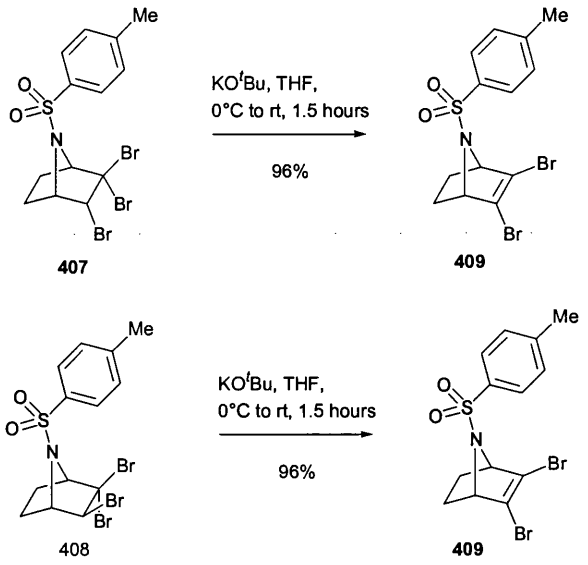
The high temperature bromination conditions were employed with an even greater degree of success for the tosyl vinyl bromide **406**.[20] Depending on the scale the reaction can be carried out in an impressive 96% total yield of the *endo* and *exo* isomers (Scheme 49). When carried out on a smaller scale this yield can drop to 90%. The ratio of the two isomers **407** and **408** was 3:2, in favour of the *endo* tribromide **407**.



Scheme 49

As with the previously prepared methyl carbamate analogues the two isomers **407** and **408** were readily separable *via* flash chromatography and the least polar isomer was judged to be the *endo* tribromide **407**, *via* the ^{1}H NMR spectra of the isomers.[29] The coupling pattern mirrors the methyl carbamate analogues. The compounds were very easy to work with as both are highly crystalline solids and are easily purified.

It was considered that the orientation of the proton might influence the reactivity of each isomer in the base induced dehydrobromination reaction to form the tosyl dibromide **409**. Especially as the norbornane system is known to favour *exo-cis* elimination, a difference in reactivity of the two isomers might well be expected. Thus each isomer was reacted separately under elimination conditions (Scheme 50). Unlike the literature procedure for the norbornane tribromide analogues **385** and **386** which used ^{t}BuOH at reflux, the best conditions for this elimination reaction were found to be KO^{t}Bu in THF at 0°C to rt.



Scheme 50

It was found that both isomers were equally efficient in this reaction. Both reactions had reached completion after 1.5 hours and both gave the dibromide **409** in an impressive 96% yield in a spot to spot reaction by TLC. The workup simply involved the filtration of the reaction mixture through a pad of silica, washed through with DCM and then concentration *in vacuo* to provide analytically pure dibromide **409**.

The dibromide was also a highly crystalline product and from a single crystal grown from DCM, an X-ray analysis was obtained. There was considerable interest in knowing the favoured position of the tosyl group. As this substrate was intended for use in the desymmetrising Suzuki-Miyaura reaction, it was interesting to see how shielded the double bond would be to the approach of the palladium catalyst system. For alkene **405** the favoured position (in solid crystal form) had been shown to be over the double bond and that the distance between the two π-systems was close enough for π-stacking interactions to take place. It was wondered whether the presence of the two large bromine atoms might change this. The

result showed this was not the case (Figure 15). The preferred geometry for the tosyl group was still parallel to the plane of the double bond.

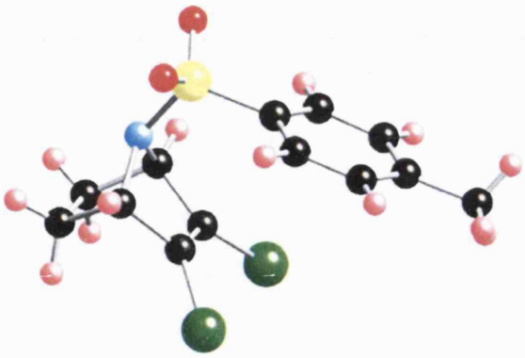


Figure 15 – dibromide 409

The distance between the carbon atoms of the double bond and the front three carbon atoms of the aryl ring, was less on average than for the bare alkene **405** (329 pm compared with 331 pm). So there was the potential for a π-interaction for this substrate also.

Like the alkene **405** the plane of the aromatic system of dibromide **409** is not aligned exactly with the rest of the molecule (Figure 16). As for alkene **405** this was assumed to be the result of a packing effect.

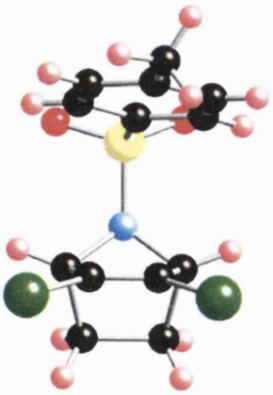


Figure 16 - dibromide 409

A view from the side shows the high degree of symmetry in the bicyclic portion of the structure (Figure 17).

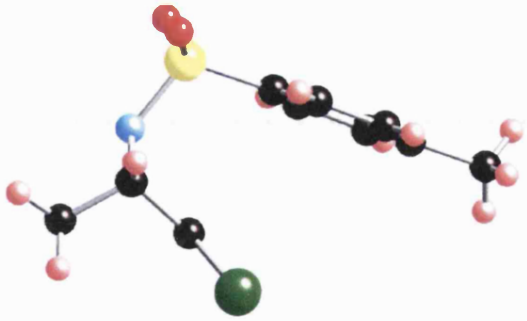


Figure 17 – dibromide 409

A study of the ^{1}H NMR spectra of all the *N*-tosylated compounds prepared (alkene **405**, vinyl bromide **406**, tribromide **407**, tribromide **408**, vinyl dibromide **409**, stannyl sulphone **412**, triaryl **467** and triaryl **468** (for the last two, see Scheme 90, Results and Discussion Part 2)) was undertaken to see if any there was any evidence for a π-stacking interaction that was suggested by the crystal structures of **405** and **409**. Ignoring the triaryl compounds **467** and **468**, there was insignificant difference in the shifts of the pair of aromatic protons adjacent to the methyl group. They appear at ~7.30 ppm for all the examples. However, the shifts of the two protons adjacent to the sulphone were noticeably different in value. In those compounds possessing an alkene the protons appear in the 7.55-7.65 ppm range. Crucially, compounds without the potential to π-stack show the protons appear in the region between 7.70-7.89 ppm.

Triaryl compounds **467** and **468** mirrored this result but also significantly show the protons adjacent to the methyl group shifted from 7.30 to 7.03 ppm. If a π-interaction is credited with the shifts in the protons, this is not unexpected given the far greater potential for π-interaction in these triaryl systems. The interaction between the π-systems of the additional aryl groups should be able to influence the protons at the back of the tosyl ring where the simple tosyl–alkene interaction was not.

Additional evidence for a π-interaction can be found in the vinyl proton shifts for the alkenes **165**, **171** and **405**. The two carbamate analogues show vinyl proton shifts of 6.16 and 6.12 ppm while in tosyl **405** the alkene proton shift is at 5.71 ppm. At first glance it may be possible to dismiss this result as just the difference in the electron withdrawing effects of the two different types of protecting groups. However, the difference between the bridgehead protons in the three compounds is negligible, 4.65 and 4.62 ppm for the carbamate analogues whereas in tosyl **405** they appear at 4.58 ppm. This would tend to suggest the difference in vinyl shifts could not be entirely due to the electron withdrawing effect of the protecting groups. This result is mirrored exactly in the three vinyl bromide analogues, methyl carbamate **399**, BOC **413** and tosyl **406**.

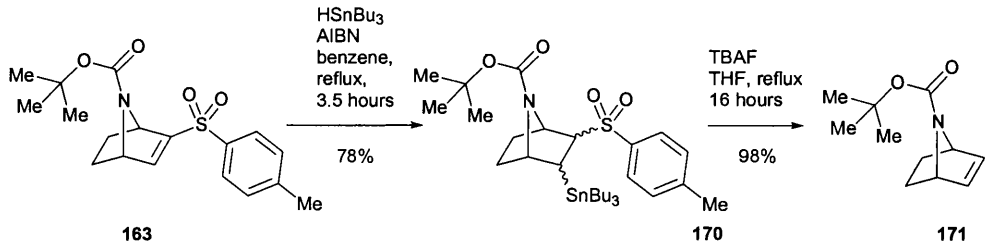
Regardless of π-interaction or not, the position of the tosyl group is once again positioned parallel to the double bond. This appears to be, for whatever reason, its preferred geometry. Although in solution it will be free to move, in this, its preferred confirmation, it will very effectively shield the top face of the double

bond to the approach of the palladium catalyst in the Suzuki-Miyaura reaction. This would hopefully provide the high degree of facial discrimination required in the desymmetrising coupling reactions.

These reactions were repeated on a larger scale with no loss of yield to provide enough material for the desymmetrising Suzuki reactions. (The tribromide isomers **407** and **408** were not separated and reacted together with no reduction in efficiency of the dehydrobromination reaction.)

Large scale preparation: the use of hydrostannylation to improve yield of alkene **171**

With the successful preparation of the dibromide **409**, the synthetic route was begun again with intention of pushing grams of material through to the dibromide. This was necessary to be able to carry out the Suzuki-Miyaura reaction trials. Now that the BOC alkene **171** was demonstrated to be readily converted into one of the other groups it was decided to concentrate on the synthesis of this compound. Also it was hoped to investigate an alternative method of sulphone cleavage that was in the literature. Carroll *et al.* reported that the BOC alkene **171** could be readily prepared in two steps from the vinyl sulphone **163** in an overall 76% yield.[33, 34] Their route involved the hydrostannylation of **163** with tributyltin hydride in the presence of AIBN in benzene (Scheme 51). This gave adduct **170** in a 78% yield. Degradation of **170** with TBAF in THF gave the alkene in a 98% yield.

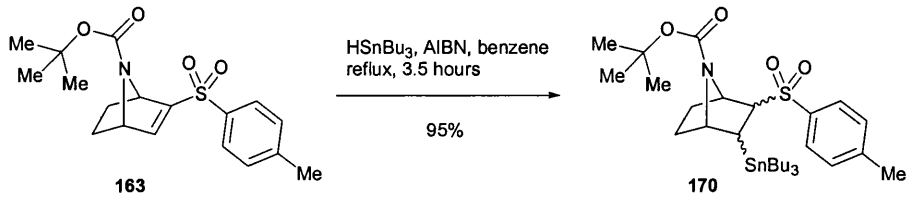


Scheme 51

The method did involve the use of toxic stannane chemistry but it was very high yielding and only involved two simple steps compared with the three used in the TMS chemistry. The alkene **171** could be prepared easily in 24 hours *via* this chemistry, and the reported conditions were performed on a 25 gram scale.[34] (Although reporting the synthesis of ten gram batches of the alkene **165** by his chemistry, Kaufmann's experimental examples are on a much smaller scale) This was too promising to ignore. Interestingly, Kaufmann in his paper reports the failure of this method in his group, as they compared the utility of both TMS and tributyltin in the anionic cleavage of the sulphone with TBAF.[21]

Initially in our hands the hydrostannylation reaction failed to yield any useful products. The tin hydride was changed to that of another manufacturer but still the reaction failed. Unluckily, both the bottles of tin hydride purchased for this experiment turned out to contain an as yet unknown tributyltin compound by about 95% weight. The hydride made up 2-5 % of the material in both bottles. Eventually some pure stannyl hydride was obtained and the reaction was attempted again. This time it was noticeable that once

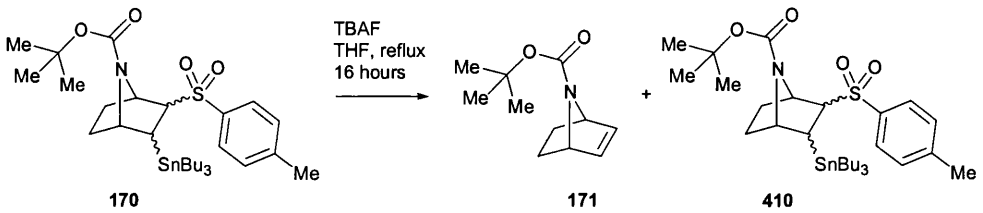
the stannane was added the reaction mixture began to bubble and foam. The reaction failed to yield any of the desired products. On consideration, it was decided that the foaming was most likely the result of metal catalysis decomposing the hydride before it had chance to react. The vinyl sulphone **163** being used was clean by ^{1}H NMR analysis, but had not been rigorously purified. The material possibly contained traces of palladium from the previous reaction step, which was the hydrogenation of the unsubstituted double bond. The material was then re-purified, first *via* filtration through silica and then using the recrystallisation conditions reported by Simpkins and co-workers using absolute ethanol.[35] This material, then analytically pure, was re-subjected to the reaction conditions and the reaction worked extremely efficiently (Scheme 52).



Scheme 52

The reaction worked in a 95% yield, significantly higher than reported in the literature. The product appeared to be a mixture of inseparable isomers by ^{1}H NMR and TLC. The exact ratio and stereochemistry was not ascertained due to the broad signals from the BOC rotamers. The mixture was subjected to the TBAF cleavage conditions without more careful study as it was assumed that the same product mixture must have been obtained in the literature and a 98% yield of the alkene was reported from the addition product.

The mixture of isomers **170** was treated with TBAF in THF at reflux for 16 hours as described in the literature (Scheme 53). The TLC at this time showed the formation of the alkene, slightly less polar than the starting material but also showed that some of the starting material remained.



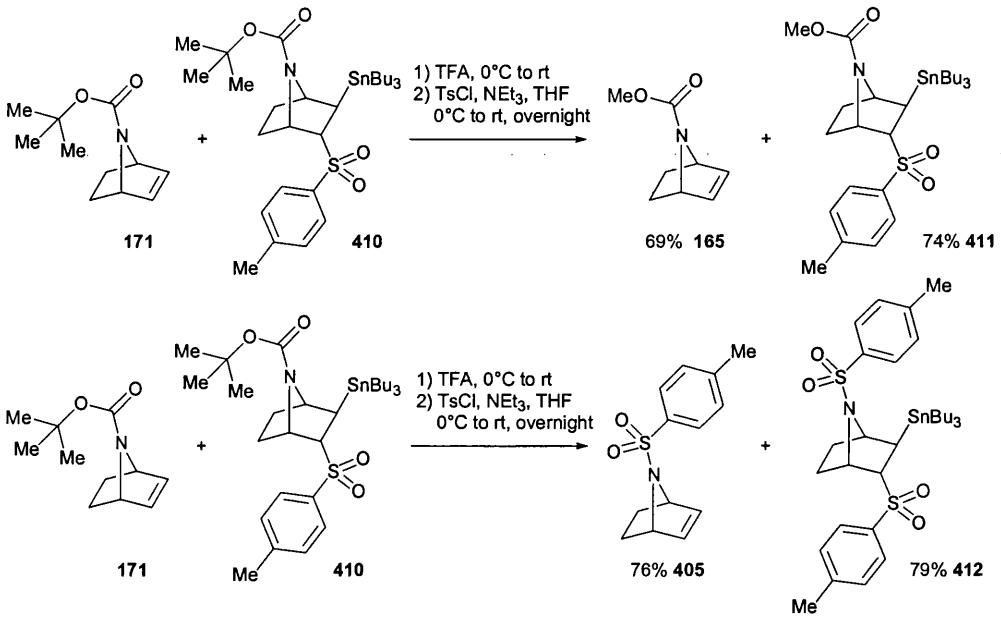
Scheme 53

Additional TBAF was added and the reaction was heated at reflux for a further 6 hours. The TLC was identical to the first. Additional TBAF was then added and again the reaction heated for a further 4 hours. After this time the reaction mixture still resembled the first TLC and the reaction was stopped and worked up. The TLC showed that the remaining starting material seemed to be a single spot, whereas before the reaction it was a group of two or more spots that had not resolved. ^{1}H NMR analysis confirmed that the

alkene had been formed and that the stannane material remaining was identical to the starting material. The ratio of the products was approximately 6:5 with the alkene being the predominant.

The stannane **410** and the alkene **171** ran too closely to separate by flash chromatography. An attempt was made but aside from a small fraction of clean alkene the rest of the material co-eluted.

It was thought that it was unfortunate that the two compounds ran so closely to each other by TLC and that it would be unlikely that the equivalent pair of compounds with either the tosyl or methyl carbamate protecting groups would co-elute. Therefore the conversion of the mixture into these analogues might allow easy separation. The mixture was converted into both methyl carbamate and tosylate protected analogues to see which one allowed for the easiest separation (Scheme 54). As both of these compounds were needed for conversion into their respective vinyl dibromides, this was considered to be a worthwhile exercise.



Scheme 54

The methyl carbamate analogues (**165** and **411**) of the mixture proved more difficult to separate that the BOC versions, the two compounds co-elute on TLC exactly. The tosylate compounds (**405** and **412**) were however separable *via* flash chromatography. The stannyl sulphone **412** solidified when purified, on standing. Examination of this material *via* 1H NMR (+ COSY) spectroscopy suggested a *trans* relationship of the two groups due to the coupling of the protons. The compound was crystallised from a DCM/hexane mixture and a suitable crystal submitted for X-ray analysis. The results showed that the unreactive isomer of the hydrostannylation reaction was the *trans exo*-stannane-*endo*-sulphone. The structure (with the hydrogens removed for clarity) viewed down the carbon-carbon bond is shown in Figure 18. This clearly depicts the *trans* orientation of the stannane and sulphone groups.

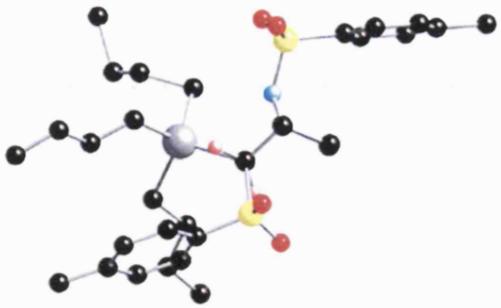


Figure 18 – stannane 412

The enantiomer of the compound in Figure 18 (also seen in the crystal) with all the hydrogens displayed is shown from an alternative perspective in Figure 19.

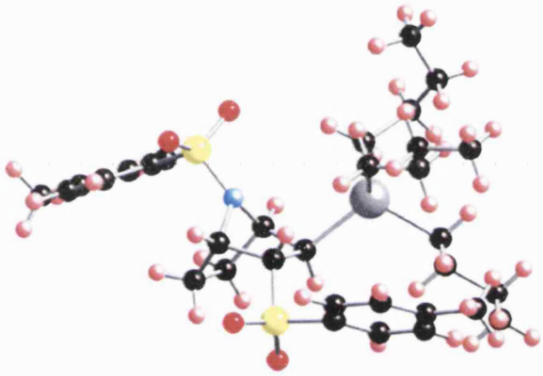
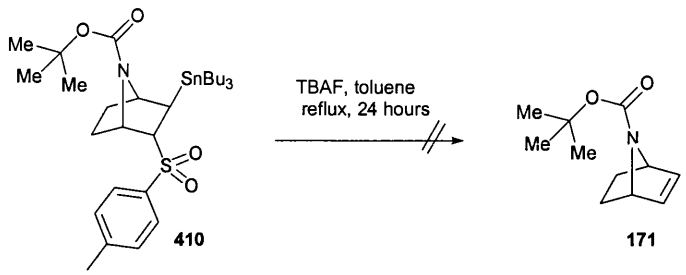


Figure 19 – stannane 412

The product that seemed to be reluctant to undergo the TBAF degradation reaction was in fact the isomer that would be predicted to be the major product. The tributyltin tin radical would attack the least hindered face of the double bond and this would be expected to be from the top face of the bicycle. The geometry at the other carbon would depend on rate at which the radical intermediate could extract a hydrogen atom. The isomer obtained is the result expected if that process is relatively slow and the substrate has had time to adopt the most favourable conformation. The *cis exo* product would derive from a rapid addition of hydrogen to the structure.

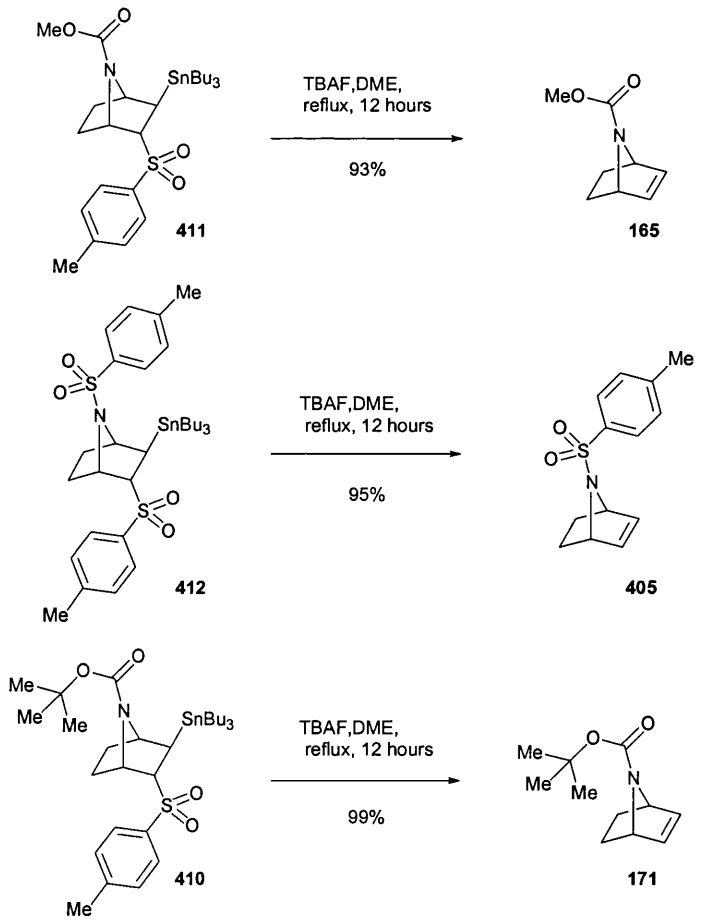
The carbamate analogues were then separated from their unreacted stannanes readily *via* vacuum distillation.

Conditions were investigated to convert the unreactive stannanes to their corresponding alkenes. The first attempt involved the use of toluene as the reaction solvent to increase the temperature of the reflux and the use of two equivalents of TBAF (Scheme 55). Unfortunately this did not induce reaction and after 18 hours produced increasing amounts of byproducts.



Scheme 55

Even at high temperatures, the reaction mixture did not become homogeneous. Toluene was replaced with DME and the reaction was repeated with the number of equivalents of TBAF increased to five. The reaction mixture was heated at reflux for 12 hours and the requisite alkene was formed cleanly in excellent yield (Scheme 56). This protocol was successfully applied to all the other stannanes.

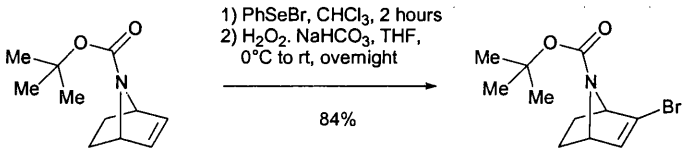


Scheme 56

The preparation of BOC dibromide **416**

It had always been hoped to prepare the BOC dibromide compound for study. The relative ease of its cleavage and removal of the additional deprotection and reprotection steps in our synthetic pathway was very attractive. The failure of the initial bromination reactions had shifted the emphasis away from the BOC series as one leading to a potential substrate. With the large scale production of this compound though it was thought necessary to try the bromination chemistry successfully proven with tosyl alkene **405**. The reticence to try the selenium chemistry on BOC alkene **171** stemmed from a much earlier trial reaction with a sample of phenyl selenium chloride which had lead to a very poor yield of desired addition product and a great quantity of decomposed products. However as the conditions of Arjona *et al.* that had been demonstrated on a BOC protected bicycle similar to ours, it was felt that the earlier reaction must have been anomalous or represent a significant difference between the chloride and bromide.

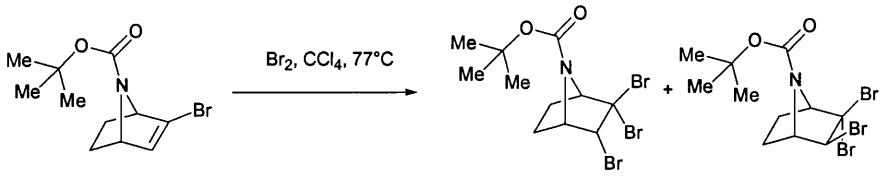
The reaction of alkene **171** with phenyl selenium bromide and subsequent oxidation/elimination of the addition product afforded, pleasingly, given the initial concerns, the desired vinyl bromide **413** in an improved 84% yield (Scheme 57).



171 **413**

Scheme 57

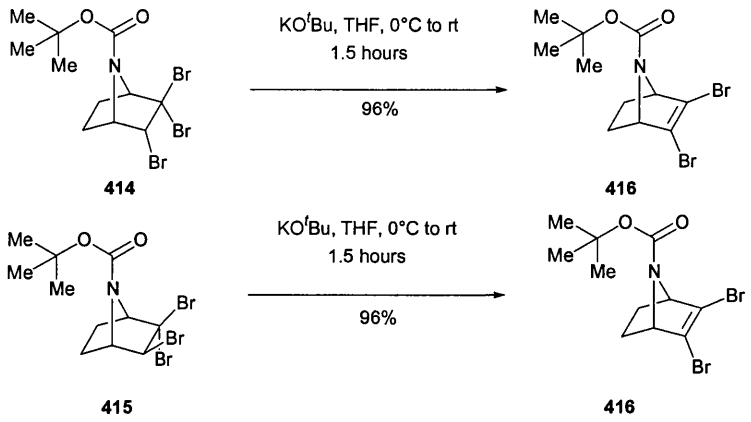
The acid sensitivity of the BOC group and the instability of the dibromide **394** led to the bromination reaction being approached with some trepidation (Scheme 58). These fears proved groundless and the tribromides **414** and **415** were obtained cleanly in virtually a 1:1 ratio from this reaction in high yield, 39% and 42% respectively. This yield was also increased to a total of 96% when the reaction was repeated on a three gram scale.



413 39% **414** 42% **415**

Scheme 58

As with their tosyl analogues, the tribromides **414** and **415** were treated with base separately to determine whether there was any difference in their kinetics or efficiency. The conditions that had worked so effectively on the tosyl analogues were repeated and gave identical results in terms of reaction times and yields (Scheme 59). Dibromide **416** could be prepared from either isomer in an excellent 96% yield.



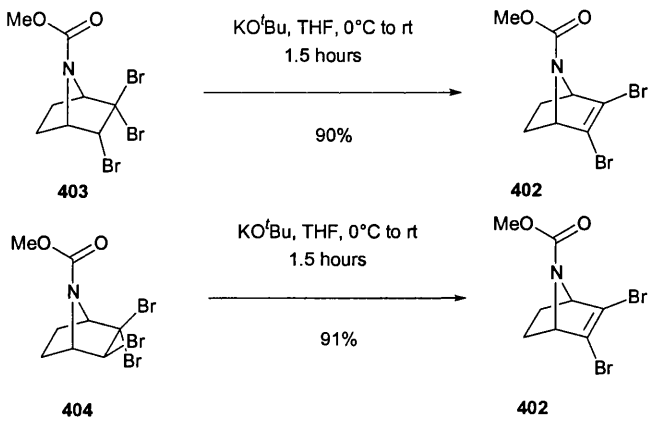
Scheme 59

The reaction sequence was then repeated on a larger scale to prepare material for the Suzuki chemistry. The tribromide isomers **414** and **415** were not separated but the dehydrobromination reaction worked equally as efficiently on the mixture. Dibromide **416** was prepared in 96% yield from the mixture on a 4 gram scale.

Preparation of methyl carbamate dibromide **402**

With the successful preparation of the both the BOC protected and tosyl protected analogues it was desired to complete the synthesis of the methyl carbamate isomer. This protecting group is the smallest of the three used and it was important to be able to prepare this compound in case it proved that the Suzuki reaction was very sensitive to the steric bulk around the double bond

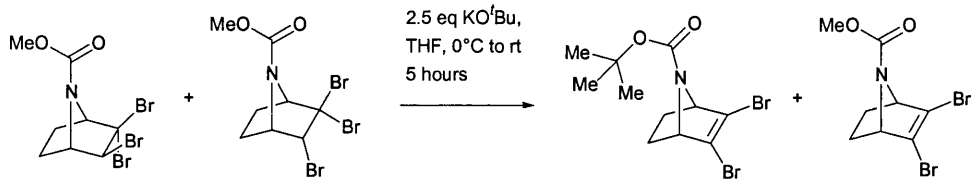
We repeated the chemistry to prepare the methyl carbamate tribromides in higher yields. In fact the reaction (Scheme 46) was carried out in an improved overall yield of 90%, with the same 2:1 ratio of products as before. The tribromide analogues **403** and **404** were also treated with KO^{t}Bu and the dibromide **402** was obtained (Scheme 60). The reactions were not quite as high yielding and were not clean, spot to spot, transformations as for the previous analogues.



Scheme 60

An unusual reaction of a methyl carbamate: conversion to the BOC product

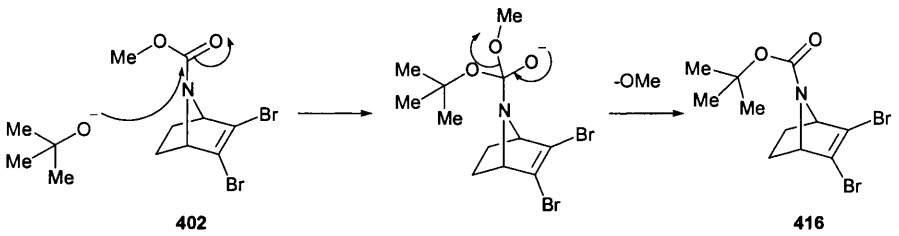
A reason for some of the reduction in yield was discovered serendipitously when a sample of the mixture of the tribromides **403** and **404** was reacted with a greater excess of KO^{t}Bu than usual and left for 5 hours instead of the required 1.5 hours (Scheme 61). The TLC after this time frustratingly revealed a major impurity had formed that was considerably less polar than the desired material and was active under ultra-violet light and *via* staining with $KMnO_4$, just as the desired product. The reaction mixture was purified and the impurity revealed as the BOC dibromide **416**, which was prepared in 48% yield in comparison with the desired methyl carbamate dibromide **402** that was formed in 41% yield



403 **404** 48% **416** 41% **402**

Scheme 61

Presumably this was forming in a *trans*-esterification type mechanism with attack on the carbonate carbon with butoxide ion followed by methoxide elimination (Scheme 62).



402 **416**

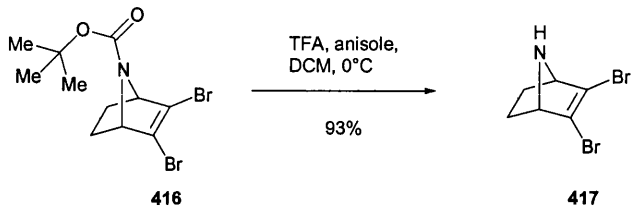
Scheme 62

This appears to be a novel transformation on a methyl carbamate. No literature examples of this process were found. The fact that it was occurring with ^{t}butoxide is remarkable in itself since it is usually not possible to generate ^{t}butyl esters in this way under *trans*-esterification conditions.

The preparation of free amine dibromide **417**

The free amine **417** was also a compound of interest for the enantioselective Suzuki reaction. The removal of any protecting group would reduce steric crowding of the double bond and therefore, theoretically at least, increase reactivity. There was also considered to be the possibility that the free amine would have a directing effect, through coordination to the Pd metal centre, to ensure approach exclusively from the top face of the double bond. Thus possibly providing the highest degree of facial selectivity of all the possible substrates.

The free amine was prepared simply from the BOC compound **416**. Deprotection was achieved in a respectable 93% yield (Scheme 63). The initial concerns (the high polarity of the secondary amine may have made flash chromatography awkward) about purification of the free amine were solved through serendipity. The crude reaction material was concentrated *in vacuo* and the desired free amine **417** sublimed from the crude reaction residue to form a colourless crystalline solid around the top of the flask.

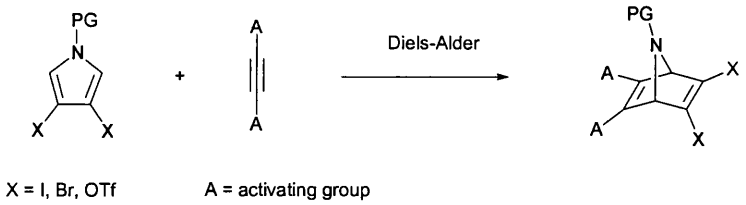


416 **417**

Scheme 63

Alternative route to aza bicyclic dihalides: the use of 3,4 dihalo pyrroles

The initial strategy to preparing the vinyl dihalides involved the use of a protected pyrrole reacting with an activated acetylene with the necessary functionality for ready conversion to the desired halides. The alternative strategy would be to prepare 3,4 dihalo pyrroles and react them with suitable dienophile (Scheme 64).

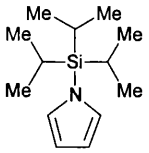


Scheme 64

The reason that this method was not tried initially is that it is much less general approach. From the iodonium acetylene it would have been possible to generate all of the [2.2.1]bicyclic systems from the one compound. This route would require the synthesis of the dihalo analogues of all the different coupling partners. Also, 3 or β-substituted pyrroles are generally hard to prepare. Pyrrole is known to react almost exclusively with electrophiles, and undergo electrophilic substitution, at the 2 or α position.

Preparation and reactions of TIPS pyrrole 418

An excellent paper by Muchowski and co-workers, on the preparation of 3-substituted pyrroles was found. This group found that the use of bulky silyl protecting group TIPS, on the pyrrole molecule **418** provided excellent β-selectivity with electrophilic substitution (Figure 20).[36]



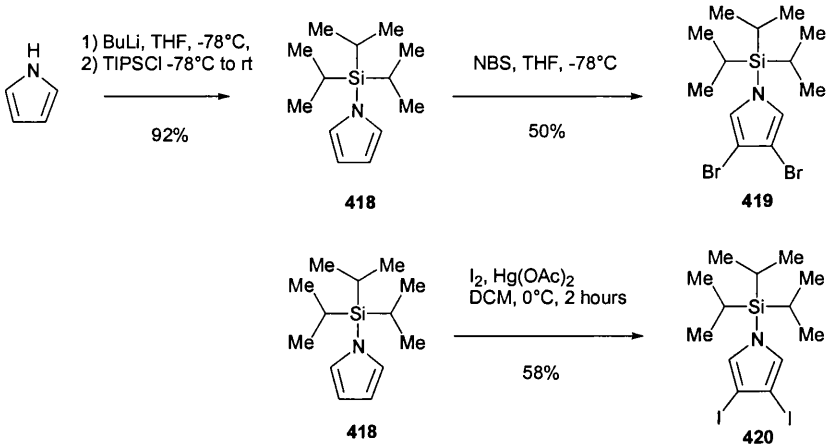
418

Figure 20

The TIPS group was shown in modelling studies to strongly block the α positions of the ring. This silyl group was also desirable because it could be cleaved readily after the completion of the electrophilic substitution reaction by simple treatment of the product with TBAF at room temperature.

Both the 3,4 diiodo **420** and dibromo **419** TIPS protected pyrroles had been prepared using this chemistry (Scheme 65). The diiodo compound had even been deprotected to give the naked 3,4 diiodo pyrrole **421**, which was a colourless crystalline solid (Scheme 66).

For the Diels-Alder chemistry, the removal of the bulky and electron rich silyl group was essential. Electron withdrawing protecting groups are essential for good Diels-Alder activity, as is unhindered access to the α carbons of the ring. For the bromine analogues this appeared to be problematic. Literature results show that brominated free pyrroles decompose in a few minutes at room temperature.[36] The TIPS compounds, **419** and **420** were prepared as shown in Scheme 65. TIPS pyrrole **418** is readily prepared from the lithium salt of pyrrole and TIPSCl. The reaction with the protected pyrrole and 2 equivalents of NBS at -78°C gave rise to a 50% yield of **419** (lit 78%) and reaction with 2 equivalents of iodine and one equivalent of mercuric acetate at 0°C prepared diiodide **420** in 58% yield (lit 69%).

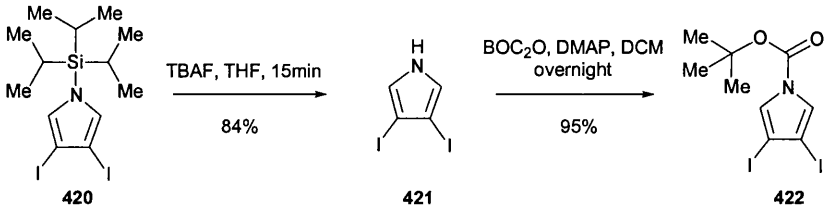


Scheme 65

The preparation of BOC diiodo pyrrole **422**

The BOC protecting group was chosen to replace the TIPS group. BOC pyrrole has been shown to be the most reactive of the protected pyrroles in Diels-Alder cyclisation reactions and the protection reaction using BOC_2O is mild and very high yielding.

The TIPS cleavage of the iodo analogue **420** using TBAF occurred readily as dictated in the literature (Scheme 66).[36] The solid free pyrrole **421** was isolated in 84% yield (lit 90%). Protection with a BOC group was then readily achieved using standard conditions (DMAP, BOC_2O in DCM), to yield protected pyrrole **422** in a 95% yield.

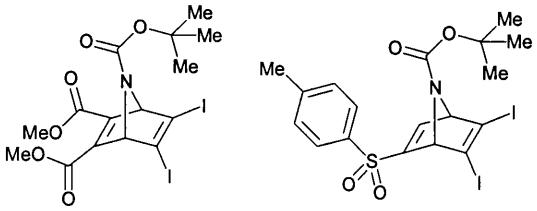


Scheme 66

The deprotection of the TIPS bromide **419** was not successful. The reaction always gave rise to decomposition products. The conversion of **419** directly into the BOC protected derivative was attempted, by adding TBAF to the compound with the BOC protection reagents in solution before the TBAF. This was not successful either. No bromine analogue of **422** was ever retrieved from the reaction mixture. The bromine analogues were deemed to unstable for further work and studies focussed on Diels-Alder reactivity of diiodo pyrrole **422**.

Preparation of diiodo bicyclo [2.2.1] adduct **423**

The acetylene of choice to test this chemistry was DMAD. Its symmetrical structure would provide symmetrical Diels-Alder adduct **423** that could be used as a model substrate in the desymmetrising Suzuki-Miyuara coupling reaction, without further manipulation. The use of the tosyl acetylene usually employed in the cycloaddition chemistry would generate **424**, which would require further steps to cleave the sulphone (made more awkward than before due to the presence of sensitive vinyl iodide functionality) to generate the desired *meso* substrates.

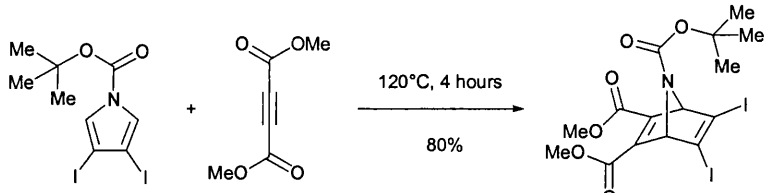


423 **424**

Scheme 67

The only concern about the use of substrate **423** in the Suzuki reaction would be in its base sensitivity. The methyl esters would limit the base used in the coupling to something mild enough to prevent hydrolysis. Fortunately there are many different examples of the Suzuki-Miyaura coupling utilising mild bases and with the substrate **423** potentially available in a single step it was too big a temptation to ignore.

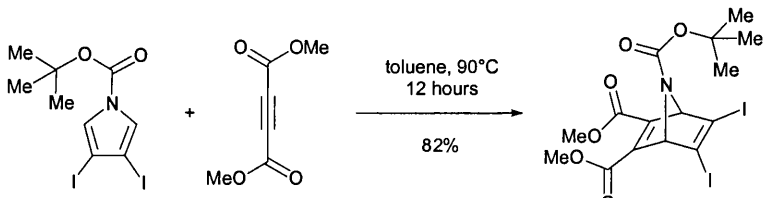
The first conditions tried were that of Traversa *et al.* in their work with BOC pyrrole and DMAD.[37] This involved the use of the pyrrole **135** in a 10 equivalent excess of DMAD heated to 120°C for 4 hours. In early work to prepare the diester **426** (Scheme 72) these conditions had been used and found to work well. These conditions were repeated using the iodo pyrrole **422** (Scheme 68) and pleasingly, on first attempt proved successful. The Diels-Alder adduct **423** was isolated after distillation of the excess DMAD in an 80% yield.



422 **293** **423**

Scheme 68

The success of this reaction led to an attempt to generate milder and cheaper conditions for its transformation. The conditions of Trudell's Diels-Alder reaction were attempted (Scheme 48, Chapter 1).[25] Using toluene as a solvent it was found that at 90°C and only two equivalents of DMAD could furnish diiodide **423** in an 82% yield in 12 hours (Scheme 69).



422 **293** **423**

Scheme 69

The vinyl diiodide was found to be crystalline and attempts were made to grow a single crystal for X-ray analysis. A crystal was grown from a DCM/hexane mixture and submitted for study. The result showed that for the diiodide **423**, the more stable rotamer was the one where the BOC group over hangs the double

bond (Figure 21). The angle of the iodine atoms from the double bond was found to be 130°, which was exactly the angle that was found for the bromines in vinyl dibromide **409**. This showed that the iodine atoms were not exerting an increased strain on the bicycle as compared with the bromine atoms.

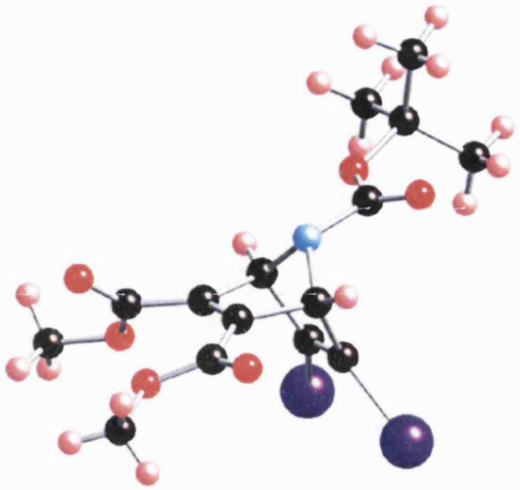


Figure 21 – diiodide 423

The view from the side shows how, in its most stable conformation, the ester and carbamate groups lie almost in the same plane, which is perpendicular to the plane of the alkene (Figure 22). This shows that there will be considerable steric repulsion to the approach of a large catalyst system to either face of the double bond. This is not an ideal situation but with the added gain in reactivity from the iodides as compared with bromides, this was not thought to be a problem.

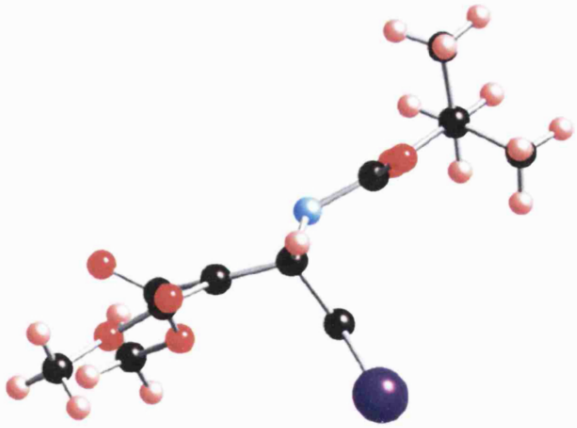
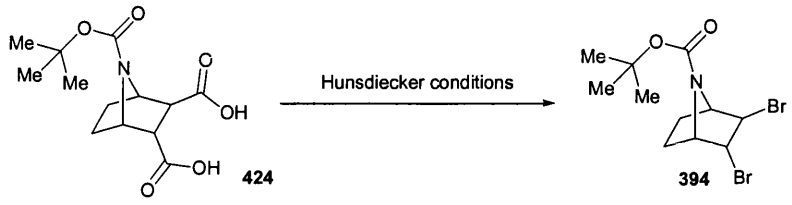


Figure 22 –diiodide 423

Miscellaneous attempts to prepare aza[2.2.1]substrates

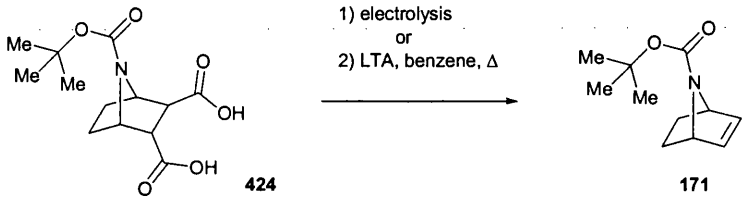
A Radical decarboxylation strategy for the synthesis of aza substrates

The alkene **171** need not be a precursor of the compounds we wish to make. The diacid **424** could potentially be treated under Hunsdiecker reaction conditions to give dibromide **394** directly (Scheme 70).



Scheme 70

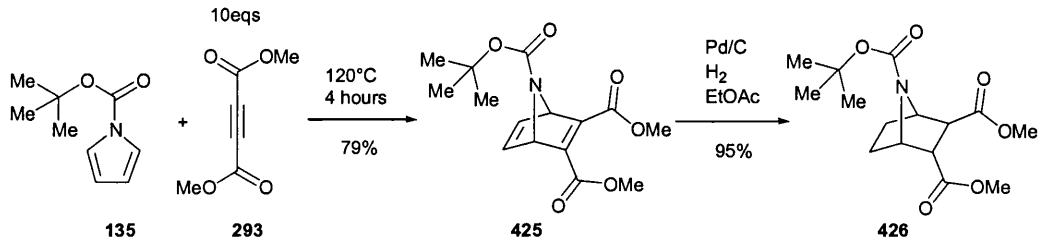
The use of *vicinal* diacids is not known and any alpha substituent is known to inhibit the reaction. If the Hunsdiecker type reactions fail, vicinal carboxylic acids can be converted to directly alkenes *via* electrolysis in a Kolbe type reaction or treatment with LTA (Scheme 71).



Scheme 71

This methodology is admittedly not high yielding but considering the ease of preparation of diacid **424** it was considered worth trying.

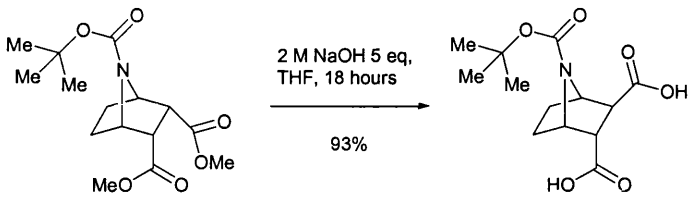
The diacid **424** can be prepared from diester **426**, which is a literature compound.[37] Diester **426** was prepared in two steps from commercially available DMAD **293** and BOC pyrrole **135**. From the diene Diels-Alder adduct **425**, a simple exhaustive hydrogenation procedure leaves diester **426**.



Scheme 72

The *cis* diester **426** was found to be readily converted to the *trans* diacid **424** with treatment of aqueous base (Scheme 73). This epimerisation process is known to occur and has been used in several syntheses of

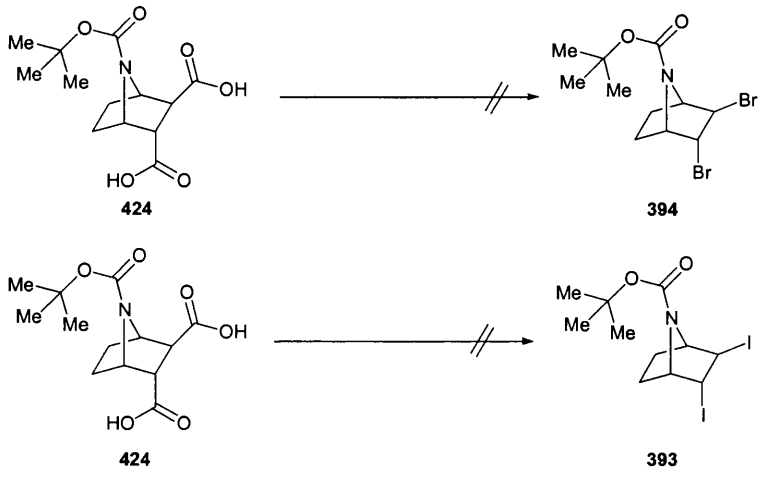
epibatidine to gain the correct *exo* orientation of the pyridyl unit. But in the case of the epimerisation of the endo epibatidine compound this process, is low yielding and requires forcing conditions. The two carbonyl groups obviously significantly increase the acidity of the protons on the ring allowing for epimerisation to occur much more readily. The diacid **424** was purely the trans isomer no *cis* diacid was obtained.



426 **424**

Scheme 73

The diacid **424** was subjected to several modified Hunsdiecker procedures (Scheme 74). The use of mercuric oxide and elemental halogen never produced any isolable products either with iodine or bromine.[38] The preparation of the Barton esters derived from *N*-hydroxypyridine-2-thione followed by radical induced decomposition in the presence of bromoform or iodoform also failed to provide any useful products.[39] The use of hypervalent iodine compound, iodosobenzene diacetate **347**, heated in CCl_4 with irradiation with white light to provide the diiodide **393** also lead to nothing.[40]

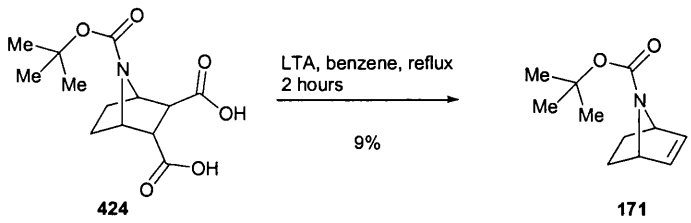


424 **394**

424 **393**

Scheme 74

The alternative oxidative decarboxylation strategy to form the alkene **171** was attempted using the methodology shown in Scheme 75.[41] The diacid **424** was treated with lead tetraacetate in benzene at reflux for two hours. While the reaction did yield some of the desired compound it was accompanied by a host (at least 10) of other products and was produced in a synthetically useless 9% yield. This result was reproduced twice before work into all decarboxylation chemistry was abandoned.



Scheme 75

Attempted synthesis of dibromide **416** *from a base induced sulphone elimination.*

Base induced elimination of sulphones is usually only achieved if the double bond formed is in conjugation with a carbonyl or other double bond. The likelihood of success would be extremely low in the case of substrate **427** with competing bromine leaving groups (Figure 23).

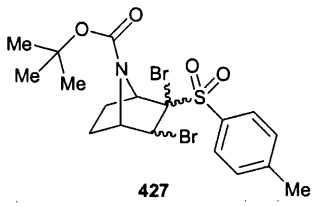
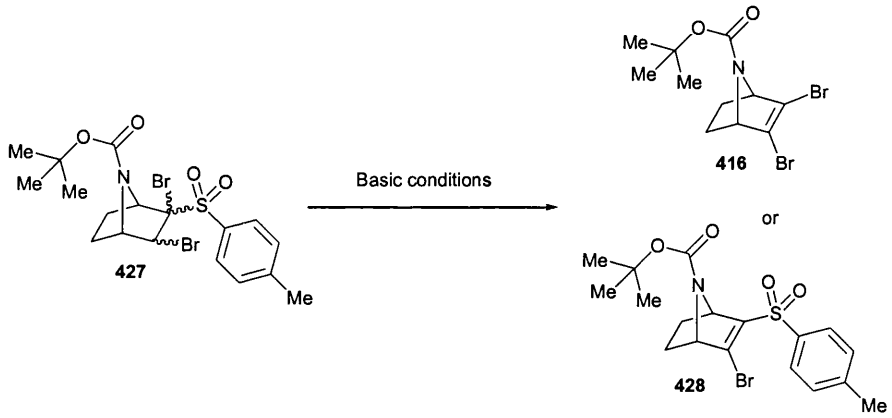


Figure 23

As dibromide **427** would be readily prepared from an intermediate, vinyl sulphone **169**, that had been prepared in a multi-gram scale several times, it was tempting to try (despite the low chances for a successful outcome). The product would be the desired dibromide and even if only low yielding this method would prove an extremely quick route to this compound (Scheme 76). Also the stereochemistry of product **427** would provide interesting information about the mechanism of the radical bromination reaction; on the vinyl bromide compound it is not possible to ascertain whether the mechanism involved a *cis* or *trans* bromination.

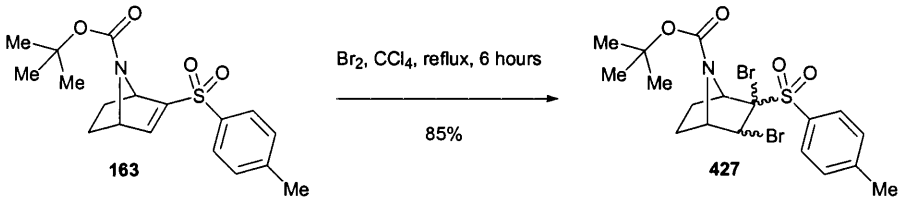


Scheme 76

The more favoured HBr elimination should dominate leading to the formation of undesired vinyl bromide **428**, as bromine is a far superior leaving group. However this may depend on the stereochemistry of the

sulphone dibromide **427**. As previously described, the mechanism for elimination on the norbornane system is almost exclusively *exo-cis*.

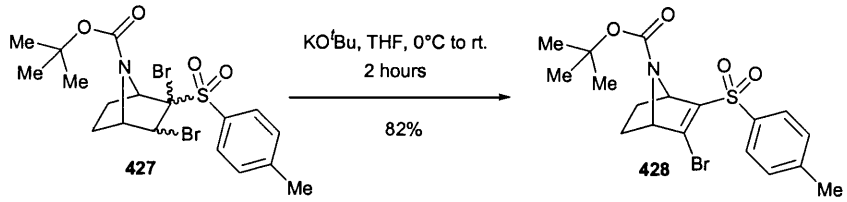
Synthesis of dibromide **427** from vinyl sulphone proved to be difficult. The deactivating effect of the sulphone prevented reaction under standard conditions of low temperature ionic bromination. Altundas and co-workers high temperature radical bromination conditions (though this time at reflux) had to be used to generate dibromide **163** (Scheme 77) but only after extended reaction times.[20] Six hours (in comparison with 10 minutes for norbornene bromide **378**) was required to give decent yield of dibromide **427**.



Scheme 77

Assignment of the stereochemistry of **427** proved impossible *via* ^{1}H NMR spectroscopy. Indeed it was not entirely certain that the compound obtained was a single isomer. The effect of BOC rotamers on the proton signals is to make them extremely broad and it was not possible even to determine the nature of the C(H)Br centre

A speculative treatment of **427** with KO^{t}Bu was attempted anyway. The result of which was only the one product, vinyl bromide **428** (Scheme 78). Not unexpectedly, no sign of any de-sulphonated products was ever seen.

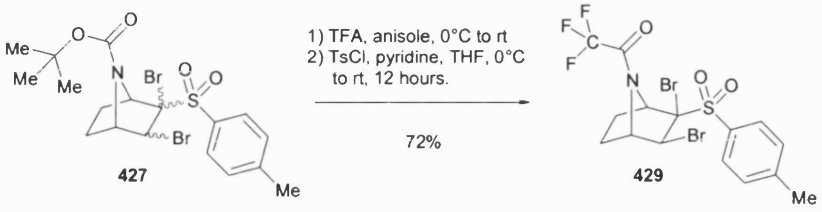


Scheme 78

Unexpected preparation of trifluoroacetamide **429**

The question of the stereochemistry of the bromination reaction was still unanswered and to try and discover its identity it was decided to replace the BOC group with the tosylate group. In our hands the tosyl group had demonstrated very sharp and diagnostic proton signals in the other bicyclic compounds prepared. This would readily allow the determination of the position of the proton geminal to the bromine. The tosyl group also provides the useful property of high crystalinity which will be necessary as

X-ray crystal analysis was needed determine the relative stereochemistry of the quaternary (tosyl, bromide) carbon. This was carried out by the treatment of dibromide **427** with TFA in the presence of anisole followed by reaction with base and an excess of tosyl chloride. The bases used were pyridine and triethylamine. In both cases the reaction provided the same unexpected product, trifluoroacetamide **429** (Scheme 79).



Scheme 79

It was not certain how this product was being formed. The same reaction conditions had successfully transformed other bicyclic BOC protected compounds into tosyl protected ones and had not shown this transformation. The BOC cleavage was certainly occurring as followed by TLC. The salt produced was somehow eliminating water under the basic reprotection conditions. The trifluoroacetamide **429** was treated with sodium carbonate in an attempt to cleave the unexpected protecting group but was not successful. More forcing (strongly basic) conditions were not tried due to the base sensitive nature of the proton alpha to the sulphone.

Trifluoroacetamide **429** was a crystalline solid and was subjected to slow crystallisation in a DCM/petrol mixture. Suitable crystals were obtained and the resulting X-ray analysis showed that the stereochemistry of the dibromide addition was *cis exo* as seen in (Figure 24). The view looking down the carbon-carbon bond shows how the bromine atoms are clearly affecting each other. The effect is similar to tribromide **404** though not as pronounced. There is a 15.7° angle between the two bromines when viewed down the carbon-carbon bond. The ring is not as puckered as for the tribromide **404**, suggesting that the tosyl group is not as sterically demanding as a third bromine atom. This view also shows how the trifluoroacetate group sits aligned to the two bridgehead carbons. The nitrogen appears to be in an almost perfect planar sp^2 hybridised state in the crystal.

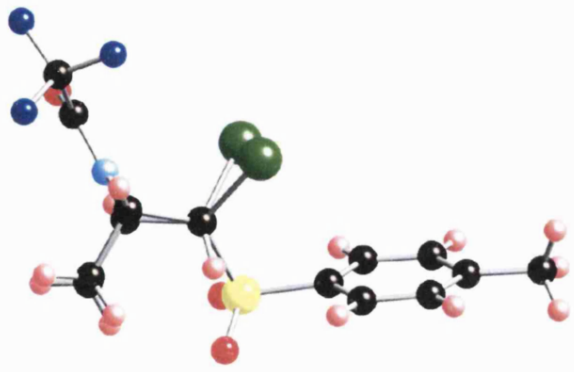


Figure 24 –trifluoroacetamide 429

The angle between bromine-carbon-sulphur is 107.4° and the plane of the toluene system is angled slightly towards the bicycle as can be seen in Figure 25.

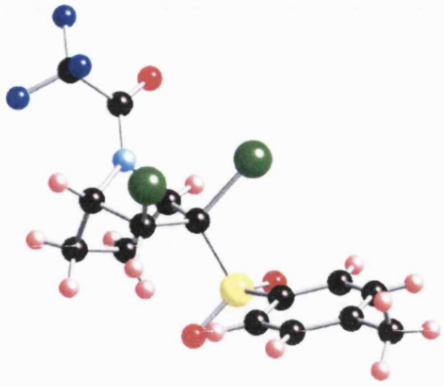


Figure 25 – trifluoroacetamide 429

The puckered nature of the bicycle is more clearly seen in Figure 26. The carbon-carbon bonds at the front and back of the bicycle are clearly not parallel and the amide bond is clearly not perpendicular to either of these two bonds.

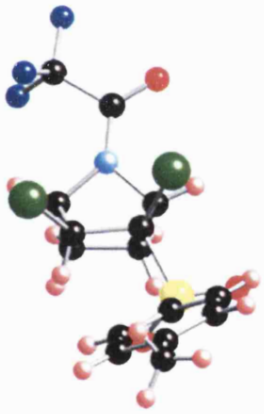


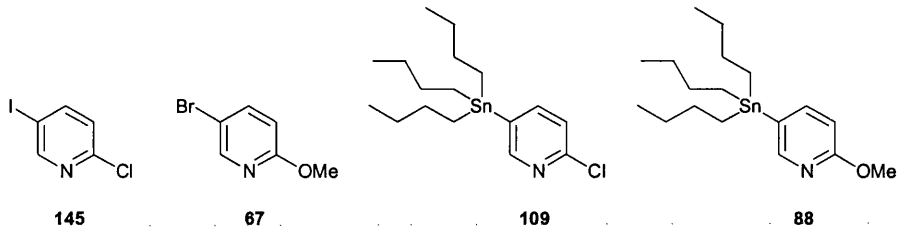
Figure 26 – trifluoroacetamide 429

Results and Discussion

Part 2 - Palladium Chemistry

Preparation of pyridyl boronic coupling partners

The chloro-pyridine portion of epibatidine, has been coupled to the bicyclic structure using iodo pyridine **145** in Heck, conjugate and nucleophilic addition chemistry (Figure 27). Stannylated pyridine **109** has also been demonstrated successfully in the Stille reaction as a precursor for introducing the chloro-pyridine unit. The methoxy derivatives **67** and **88** have also been prepared and successfully used by groups who found the chloro pyridine moiety too sensitive to survive their syntheses.

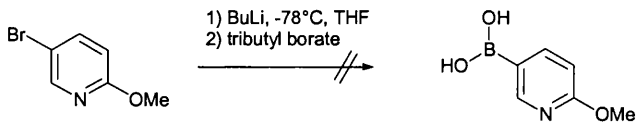


145 **67** **109** **88**

Figure 27

To date, there has been no published synthesis of epibatidine that utilises Suzuki chemistry to introduce the pyridine unit. The necessary boronic pyridines are not commercially available. Compared with the vast array of phenyl substituted boronic acids commercially available to the synthetic chemist, there is a real dearth of substituted pyridines. Those that are available are usually boronic esters rather than acids. Suggesting that there is considerable difficulty in either preparing or purifying pyridine boronic acids. Purification looks difficult on first glance due to the amphoteric nature of the compounds. The acid functionality should provide basic solubility and the pyridine should ensure acid solubility. The high melting points of boronic acids usually rules out distillation as a purification method.

The reaction of bromopyridine **67** (prepared *via* the method of Tee [42]) with BuLi followed by quenching with tributyl borate was attempted. However, despite disappearance of starting material no product was ever successfully isolated from the reaction mixture (Scheme 80).

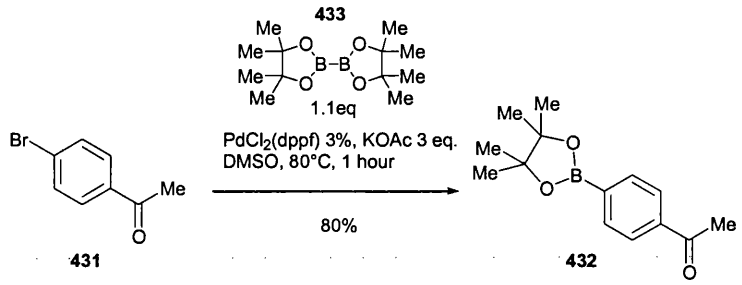


67 **430**

Scheme 80

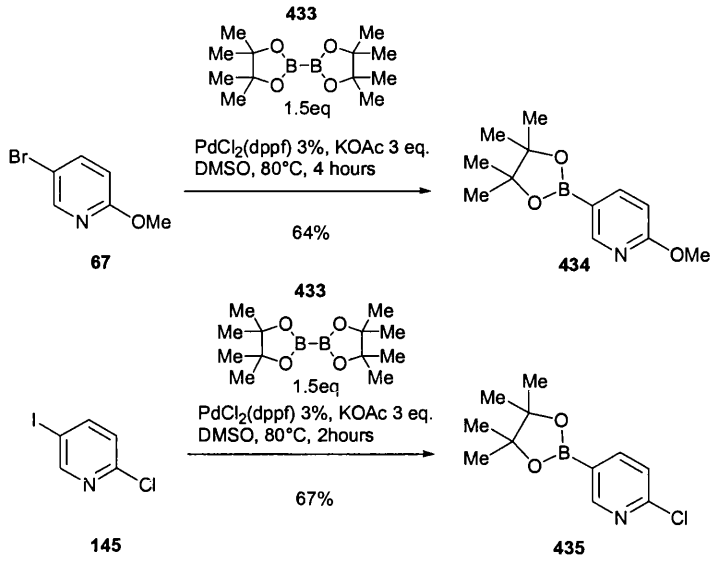
Alternative methods for the preparation of the required pyridine boronates were investigated. In particular it was hoped to prepare a boronic ester rather than acid to aid the purification. Boronic esters have a much lower melting point than their related acid. This allows for a distillation method of purification and prevents the acid/base extraction problem.

The simplest and most effective method appeared to be that of Miyaura *et al.* Their method utilises diboron ester **433** in a coupling with aryl iodides and bromides to prepare the pinacol boron ester derivatives that are purified *via* Kugelrohr distillation. An example is shown in Scheme 81. The key to the reaction was to tune the conditions to only favour the diboron coupling and not the potential coupling between the aryl bromide and freshly prepared aryl boronic ester. This was achieved by the use of weak base KOAc, which was found to successfully minimise this undesirable second reaction.



Scheme 81

These conditions were carried out on bromo pyridine **67** and a commercially obtained sample of iodo pyridine **145** (Scheme 82). The reactions were repeated as in the literature except using an increased excess of the diboron ester **433**. The reactions were not optimised, as there was no time available to repeat them. The reactions were successful but the excess diboron compound was present in both the products after Kugelrohr distillation. Both the compounds were isolated with 70% purity. The yields quoted are based on the ratio of intensity of the ^{1}H NMR signals. No attempt was made to purify *via* flash chromatography, as it was not certain that the boron ester would survive intact. The chloride **435** was successfully used crude in a Suzuki-Miyaura reaction with BOC-dibromide **416**, *vide infra.*



Scheme 82

The preparation of novel enantiopure monodentate phosphine ligands from C_2-symmetric bidentate diphosphines

Monodentate phosphine ligands have been shown to be increasingly more active in cross-coupling chemistry than bidentate examples. The groups of Fu and Buchwald now use monophosphine ligands as a matter of routine (Figure 28).[43, 44]

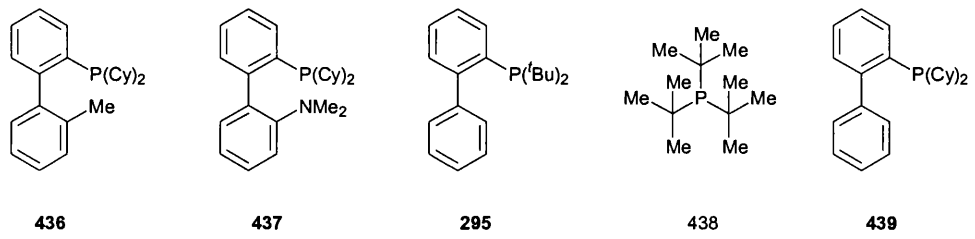


Figure 28

Chiral versions are not so readily available however although Buchwald has reported the binaphthyl versions of biphenyls **436, 437, 295** and **439** they are not commercially available and their synthesis is not trivial.[45] A commercially available chiral monophosphine that has been successfully used in the literature by Hayashi's group and by our own group is MeO-MOP **334** (Figure 29).[46-48]

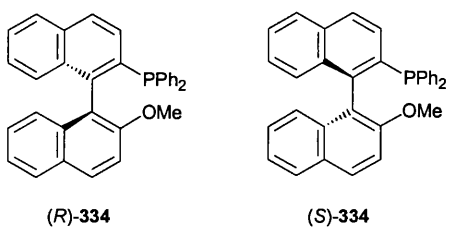
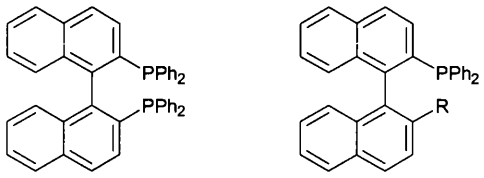


Figure 29

Unfortunately, MOP is currently extremely expensive. One hundred milligrams of either isomer will cost £200.

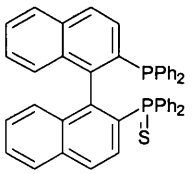
Given the very high cost involved, it was hoped to prepare monodentate phosphines from cheaper C_2-symmetric diphosphines. BINAP is the most widely used C_2-diphosphine and is available for approximately one thirtieth the cost of MeO-MOP **334** by weight. Currently £60 will buy one gram of either enantiomer of BINAP **440** (Figure 30). If one of the phosphines could be inhibited in some way then a MOP equivalent **441**, could be prepared for a fraction of the cost.



440 **441**

Figure 30

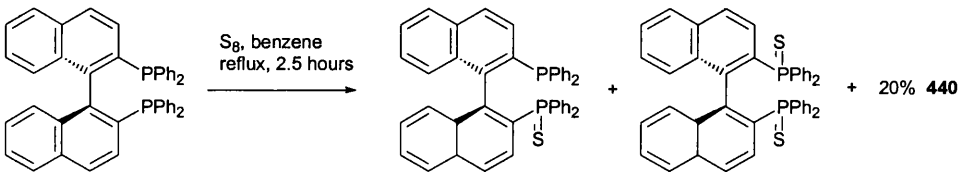
The reaction chosen to reduce the binding affinity of the second phosphine was a sulphide formation reaction, to produce sulphide **442**. This will reduce the electron density at the phosphorus atom as well as increasing the steric bulk around it. These combined effects should reduce the capacity of the phosphorus atom to bind to a metal centre.



442

Figure 31

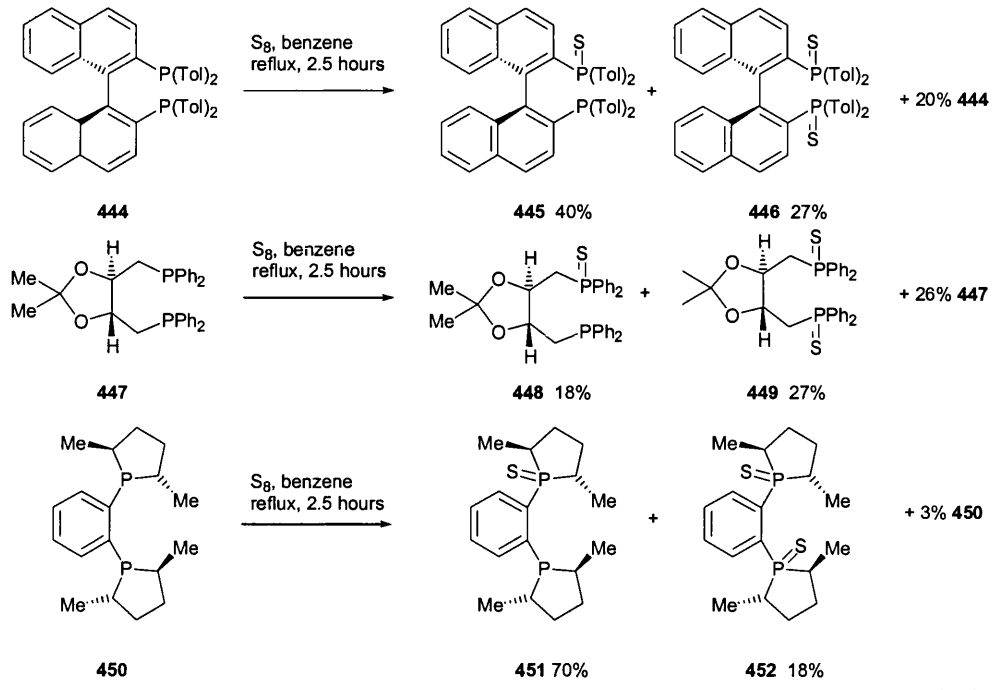
As BINAP is C_2-symmetric there is no control over the reaction. The most likely result is a statistical mixture of the starting BINAP **440**, the mono phosphine sulphide **442** and the *bis* sulphide **443**. The reaction was carried out with (*R*)-BINAP **440** in benzene using elemental sulphur as the reagent (Scheme 83). With 1.2 equivalents of sulphur the *mono* and *bis* adducts were obtained in 37% and 27% yields respectively. 20% of starting material, (*R*)-BINAP **440**, was also recovered.



440 37% **442** 27% **443**

Scheme 83

The same chemistry was applied to the ligands (*R*)-DIOP **447**, (*R*)-Tol-BINAP **444**, and (*R*)-DUPHOS **450**, to prepare the analogous *mono* and *bis*-sulphides (Scheme 84).



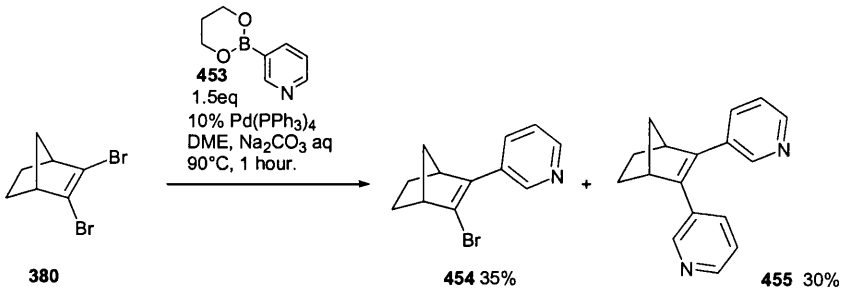
Scheme 84

All the sulphides were prepared in yields shown on Scheme 84. The ratio of the *mono* and *bis* products formed varied between the substrates. DUPHOS providing the best ratio of yield of the mono adduct over the *bis* adduct. The low yields for the sulphide reaction for (*R*)-DIOP **447** should be not be viewed too negatively. The sample of DIOP used was small and old and in the TLC of the reaction mixture it was clear to see that there were additional products. Presumably this was some of the oxide product, as well as some mixed sulphide and oxide. Starting material was recovered in all cases.

Suzuki-Miyaura chemistry of 1,2 dihalo substrates

Coupling chemistry of norbornene 2,3 dibromide 380

The first desymmetrising substrate that was tested with the desired Suzuki-Miyaura coupling chemistry was norbornene dibromide **380**. This substrate could be made in substantial quantities in four straightforward steps from norbornene. The first reaction attempted was using Suzuki's original conditions for aryl boronic acid coupling; tetrakis triphenylphosphine palladium and aqueous sodium carbonate as the base. Pyridine 3-boronic ester **453** was chosen as the coupling partner (Scheme 85). The reasons for this choice were two fold, one its similarity to the aryl fragment of epibatidine and two, its polarity. The main difficulty in the handling of these halo norbornene/norbornane substrates had been caused by their lack of polarity. Flash chromatography being more akin to a rapid filtration as the R_f's of these compounds were all over 0.7 in pure petrol.



Scheme 85

The initial result was pleasing; using 1.5 equivalents of the boronic ester **453** the mono adduct **454** was obtained in 35% yield and the *bis* pyridine **455** in 30%. This corresponded to a near perfect mass balance with the boronic ester, and in virtually a statistical mixture. The starting material was not recovered after the reaction due to its non-polarity it was difficult to isolate it in a pure enough form to obtain data on its remaining quantity.

Unfortunately the original result, in terms of ratio of the two products, was never repeated. In future reactions the yield of the *bis* adduct **455** increased to the detriment of *mono* **454**. The *mono* product was formed in 10-15% and the *bis* product 45-55%. Possibly this was due to the change in source of tetrakis triphenylphosphine palladium used. The initial reaction was carried out while in industry on placement, using a freshly prepared batch and the repeated reactions were with commercially available material. After the first few reactions tetrakis was abandoned in favour of $Pd(OAc)_2$ or $Pd_2(dba)_3$ with two equivalents of PPh_3 as the standard racemic catalyst system used. This was found to be a more consistent and reliable catalyst than the sensitive tetrakis.

The reaction was carried out with five other aryl boronic acids to see how general this reaction was. Both electron rich and poor acids were tested (Figure 32).

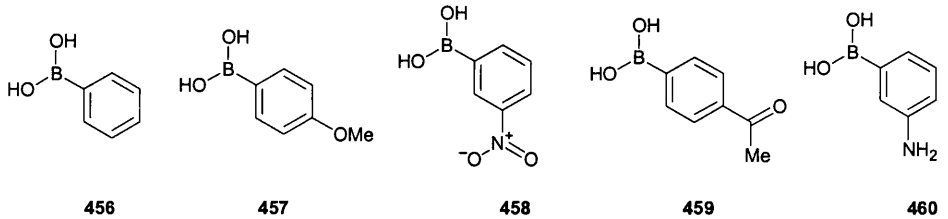
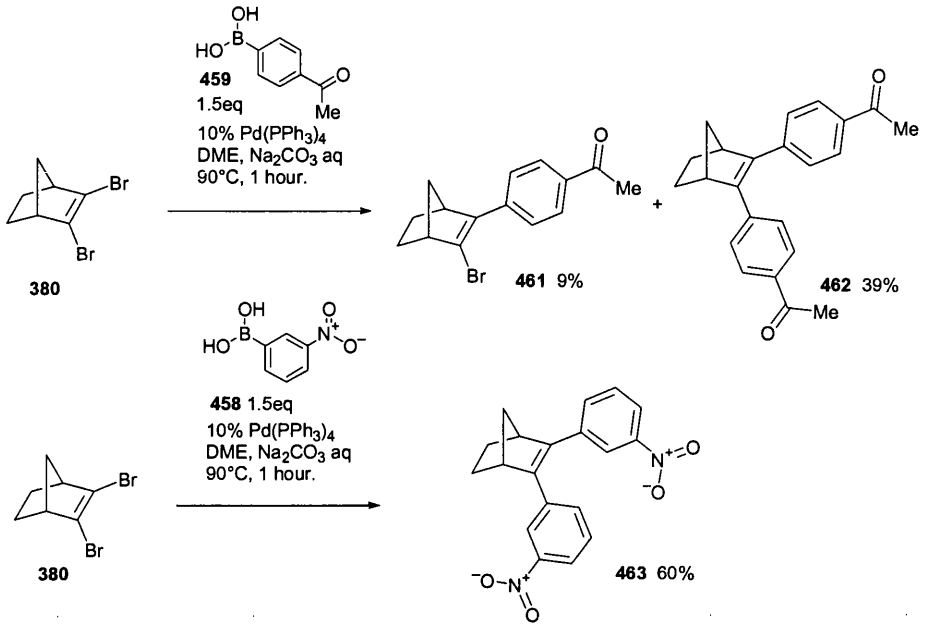


Figure 32

The reactions were successful apart from the 3-amino derivative **460**. In the majority of cases problems came with purification. The benzene **456** and 4-methoxy benzene **457** boronic acid products were too difficult to purify due to their lack of polarity; despite the crude ^1H NMR spectra showing useful conversions, these compounds were not isolated. However 3-nitro **458** and 4-acetyl **459** benzene boronic acids both gave reaction products that were readily separable (Scheme 86). The acetyl boronic acid gave

rise to both the *mono* **461** and *bis* adduct **462** with the *bis* adduct being the predominant product. A yield of 39% of the *bis* substrate **462** was isolated to only 9% of the *mono* compound **461**. For the nitro boronic acid only *bis* adduct **463** was produced during the reaction in a 60% yield.



Scheme 86

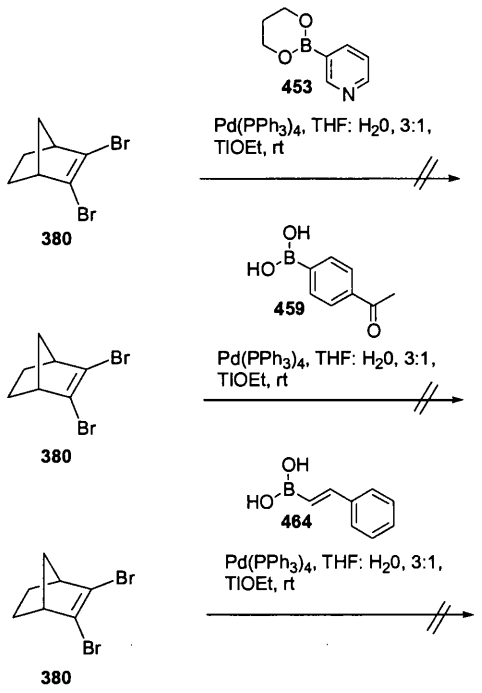
The trend that seemed to be emerging from the initial reactions is that electron poor aryl boronic acids appeared to activate the remaining bromide to a second coupling reaction. From pyridyl through to nitro a decline in the amount of *mono* coupled product was seen. The yields were not very high and the reactions were not very clean. TLC showed the formation of many minor products as well as the desired products and it was often difficult to obtain clean samples of the coupled products

It was chosen to examine the 4-acetyl boronic acid reaction further as the pyridyl boronic ester was much more expensive and less readily available. The highly polar nature of the pyridine compounds also made them less attractive for the HPLC analysis required for the determination of enantioinduction in enantioselective syntheses.

The first modification that was made to the reaction was to attempt to reduce the temperature. The reaction was repeated at room temperature with different solvents (DME, THF, Benzene, dioxane) and with a variety of different aqueous bases (KOH, Cs_2CO_3, Na_2CO_3) and non-aqueous bases (KF, CsF). The reaction was either nonexistent or extremely low yielding under these conditions.

The reaction conditions of Frank *et al.* were also employed. Using commercially available thallium ethoxide as a base, Suzuki-Miyaura couplings could be carried out at room temperature in THF (Scheme 87).[49] The conditions were noted to be much more effective when used in conjunction with a vinyl boronic

acid rather than an aryl one. The reason for this was supposed to be one of solubility of the intermediate thallium borate complexes. The reactions were run with high excesses of the boronic acids. Often five equivalents were used.



Scheme 87

In the case of the norbornene dibromide **380** unfortunately the use of thallium ethoxide resulted only in the decomposition of the reaction mixture, which turns from bright yellow to black in 5-10 minutes with only traces of coupled products seen by TLC. This was regardless of the number of equivalents of the boronic acid used or the nature of the catalyst system. $Pd(PPh_3)_4$ was replaced with $Pd(OAc)_2/2PPh_3$ with no effect.

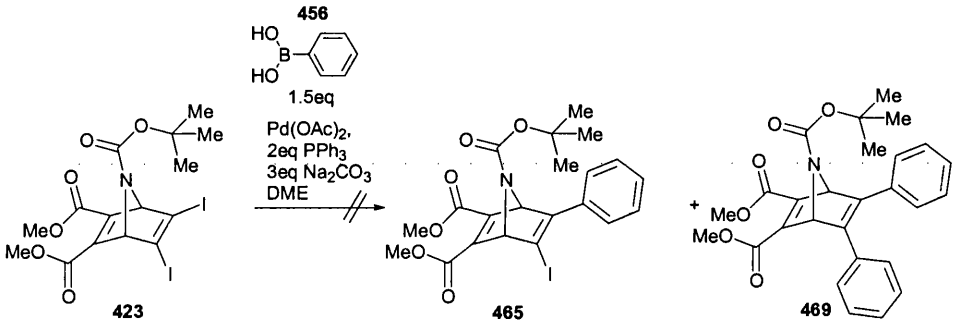
Conditions to separate the *mono* product **461** into its enantiomers *via* chiral HPLC were found but enantioselective reactions were not attempted. The lack of *mono* products formed with this substrate was disappointing and it was felt that time would be better spent trying to develop the synthesis of the nitrogen system substrates which were not yet prepared at this time.

The substrate **380** had provided useful information as to the synthesis of the nitrogen analogues and had shown that the 1,2 dibromide system was reactive in Suzuki chemistry. The preponderance of *bis* products formed in this reaction was disappointing although the use of an enantiomerically pure catalyst would hopefully limit this.

Attempted Suzuki-Miyaura coupling of diiodide **423**.

The first of the aza[2.2.1]bicycle substrates prepared was diiodide **423** and thus it was the first one to be tested under Suzuki coupling conditions. The methyl esters presented a limitation on the range of bases that could be tested although fortunately the most reactive conditions for the norbornene dibromide obtained Na_2CO_3. This was thought to be a mild enough base to prevent hydrolysis of the ester functionality and cause the additional complication of gaining a mixture of hydrolysed and non-hydrolysed products.

The diiodide **423** was reacted under the standard Suzuki conditions with Na_2CO_3, DME at 90°C with phenyl boronic acid **456**. The catalyst system used was $Pd(OAc)_2$ with two equivalents of triphenylphosphine. The reaction was not successful even after 6 hours at 90°C, with no products from the Suzuki coupling being observed (Scheme 88).



Scheme 88

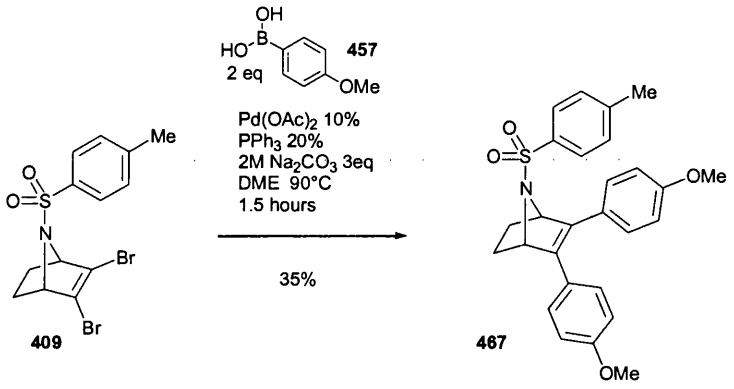
This reaction was repeated and also the boronic acid changed for the 4-methoxy and 4-acetyl benzene boronic acids **457** and **459** with no reaction being seen in either case. Somewhat surprisingly, the diiodide **423** was recovered from the reaction mixture in each case in respectable yields (50-80%, depending on the length of the reaction) and seemed to be quite stable to the reaction conditions.

This result was extremely disappointing. The diiodide was presumed to be the more active substrate and it demonstrated a complete lack of reactivity. This was presumed to be due to steric parameters. The bulky tetra-substituted alkene was just too hindered for the approach of the palladium catalyst system. The X-Ray structure obtained of diiodide **423** had showed just how crowded the iodide double bond of the molecule was (Figure 22) and this seemed to have been borne out in the lack of reactivity shown. No further modifications were made to gain reactivity as the first of the aza dibromide substrates, tosyl **409**, was prepared at this time. Attention was then focused on the Suzuki-Miyaura couplings of this less limiting substrate.

Coupling chemistry of tosyl dibromide **409**

The first of the aza[2.2.1] bicyclo dibromides to be synthesised in sufficient quantity to investigate some Suzuki chemistry was the tosyl-protected analogue **409**. Disappointingly, the substrate proved highly resistant to reaction at room temperature. The thallium ethoxide conditions failed to provide significant reaction,[49] as did the modified conditions of Fu ($Pd_2(dba)_3$, $P(^tBu)_3$, THF, KF) Scheme 7, Chapter 2)[44] and Buchwald ($Pd(OAc)_2$, phosphine **295**, THF, KF, Scheme 6, Chapter 2).[43] The reactions succeeded only in yielding vary quantities of the substituted biphenyls (boronic acid homo coupled product). The starting dibromide was recovered from all these reactions in greater than 50% yields.

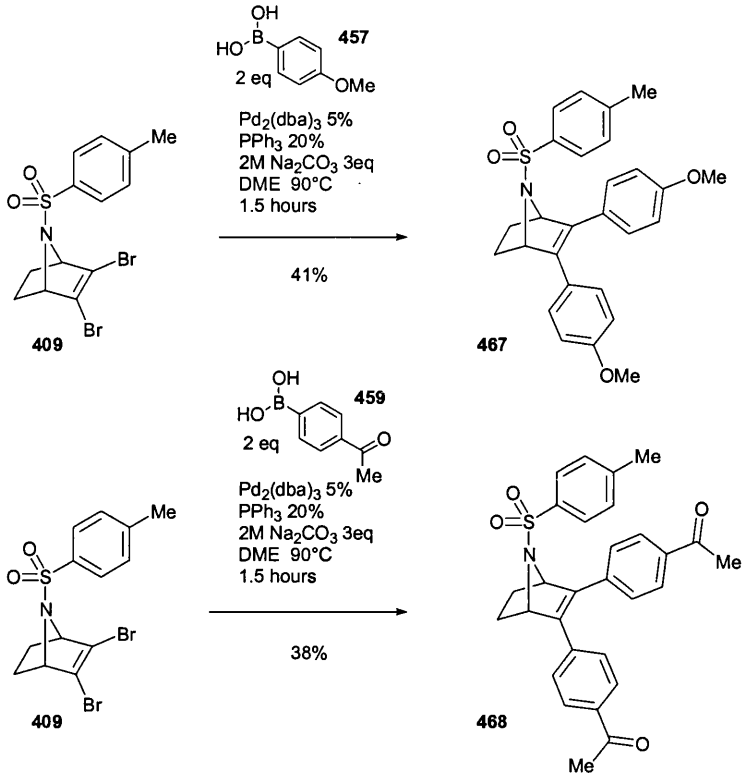
To try to attain any products the standard conditions of Suzuki in DME were used with 4-methoxy benzene boronic acid **457** and a Pd(II) source in the form of $Pd(OAc)_2$ as a coupling partner at 90°C (Scheme 89).[50]



Scheme 89

The *bis* coupled product **467** was obtained in low yield. TLC showed no *mono* product in the reaction mixture. Less than 5% of the starting material remained. Obviously this was not an encouraging result. For high enantioselectivity it was hoped to gain reactivity at low temperatures. A 35% yield of the doubly coupled product and no *mono* compound after 90 minutes at 90°C showed that this was going to be difficult to achieve.

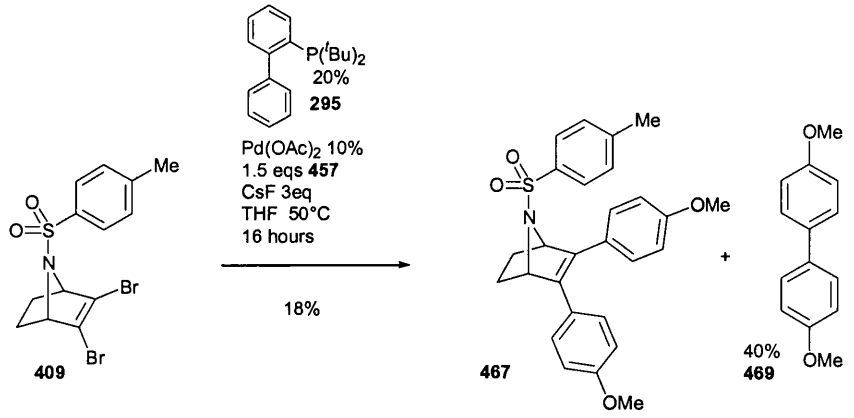
The reaction was repeated using a Pd(0) source in the form of $Pd_2(dba)_3$ with 4-acetyl **457** and 4-methoxy **459** boronic acids, to see if this would aid the reactivity (Scheme 90).



Scheme 90

The general reactivity of the substrate at this temperature and conditions was confirmed, with both *bis* coupled products being obtained in similar low yields. The change in palladium source did provide a slight increase in yield of *bis* anisole **467**. The change in palladium source also provided a trace of the *mono* compound for the 4-methoxy benzene boronic acid reaction. The mono product was not clean enough to obtain data and was found (as the norbornene mono-coupled products) to be fairly unstable. Significant decomposition occurred overnight if left at room temperature.

The conditions of Buchwald were attempted at elevated temperatures in an attempt to increase the yield of products.[43] With the reaction in THF the temperature was limited to 50°C to avoid reflux or significant solvent loss. The greatest yield of *bis* product obtained was 18% in the conditions outlined in Scheme 91. Once again, a trace of *mono* product was obtained though not clean enough and not in sufficient quantity for data to be collected.



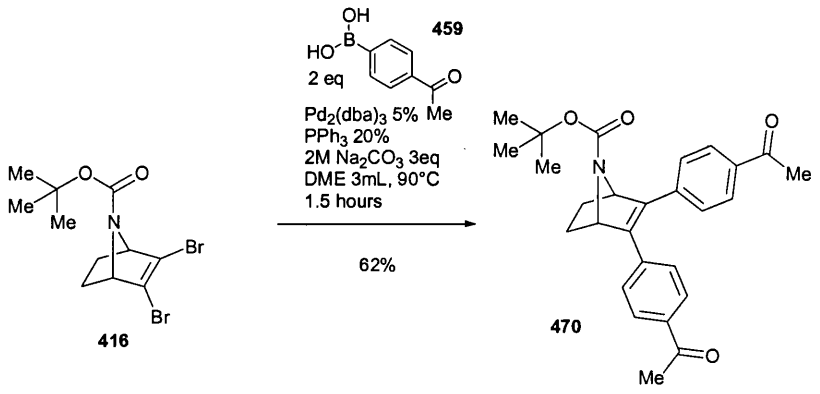
Scheme 91

The reaction still produced significant quantities of the homo coupled boronic acid, which was still the major product.

Suzuki coupling chemistry of the BOC dibromide **416**

The BOC dibromide was prepared after the initial reactions had been carried out on the tosyl analogue and it was hoped that it would offer some increased reactivity in the coupling chemistry. This was predicted because the BOC group cannot π-stack with the double bond. It has been shown that the tosyl group completely shields the top face of the alkene as seen in the crystal structure of both the dibromide **409** and alkene **404** (Figures 15 and 12). This effect is proposed to be due to a π-interaction between the tosyl aryl system and the double bond. The BOC group does not possess a π-system that can interact with the double bond and therefore from a purely steric perspective, the carbamate protected analogue **416** should be more reactive to the coupling reaction.

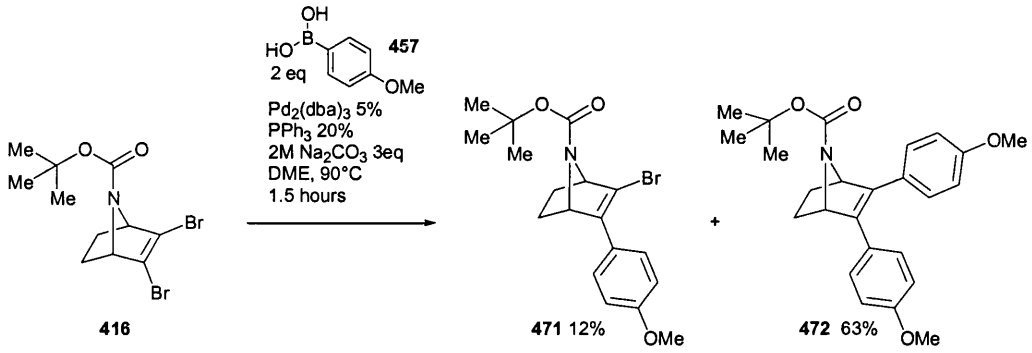
The first reactions attempted were those that had provided the highest yield when used with the tosyl compound **409**, namely the standard conditions of Suzuki utilising $Pd_2(dba)_3$ and two equivalents of PPh_3. The reaction was attempted with the boronic acid **459** (Scheme 92).



Scheme 92

The reaction only provided the *bis* coupled product **479** as it had for the tosyl analogue **409**. The reaction however did proceed to give a much more respectable yield of the doubly coupled product **470**, which was isolated in 62% yield.

When the same reaction conditions were applied using the 4-methoxy benzene boronic acid **457** (Scheme 93) however, a significant quantity of the *mono* adduct **471** was isolated along with the predominant *bis* product **472**. The combined yield was respectable and showed significant improvement over the tosyl analogue.

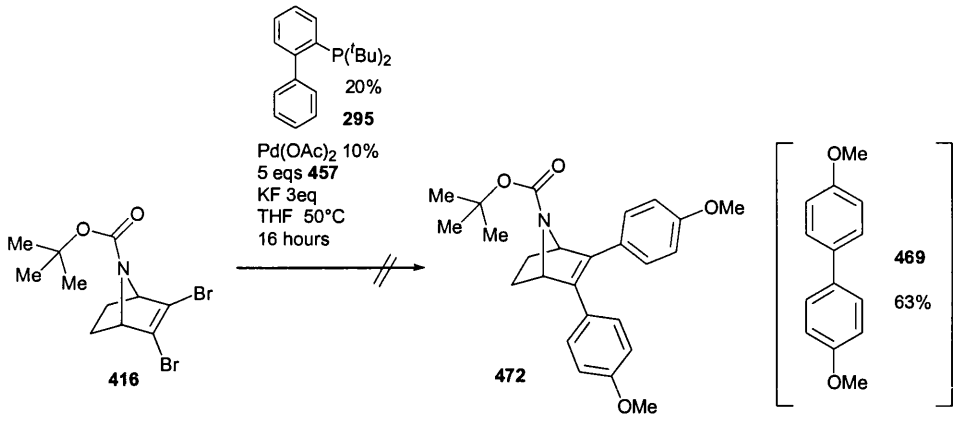


Scheme 93

The production of the *mono*-coupled product **471** when using the methoxy benzene boronic acid **457**, again suggests that electron rich coupling partners reduce the reactivity of the second vinyl bromide to oxidative addition.

The reactions in Schemes 92 and 93 were repeated at 60°C to see if the reaction could be performed at a lower temperature. The drop in reaction temperature reduced the yields of the products to 23% of *bis* methoxy **472** and 29% of *bis* acetyl **470** product. Also the *mono* coupled product **471** was not produced at all.

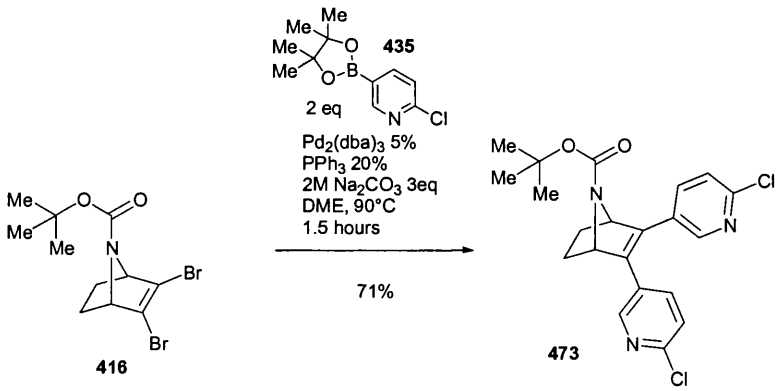
The Buchwald conditions at elevated temperatures were tried with several different ligands and different bases as well as using a large excesses of the boronic acids (Scheme 94).[43] However none of these conditions provided significant product and all provided homo-coupled boronic acids as the major products. These conditions seemed to promote this coupling. In the example below, using 5 equivalents of the 4-methoxy boronic acid **457**, the homo coupled *bis* anisole **469** was obtained in 63% yield.



Scheme 94

The Suzuki-Miyaura reaction of chloro-pyridine boronic ester **435**

Given that we had prepared the epibatidine precursor pyridine boronic ester **435** it was felt that it was necessary to test its reactivity in the Suzuki reaction (Scheme 95). Even though it had not been purified and still contained 30% of the diboron species **433** (2 equivalents of the pyridine were based on its purity by ^{1}H NMR spectroscopy) the reaction produced the *bis* pyridine **473** in a respectable 71% yield. This proved that the pyridine ester was a viable and high yielding coupling partner in the Suzuki-Miyaura reaction. Providing a suitable catalyst system can be found to promote *mono* product formation, a route to epibatidine is possible with pyridine boronic ester **435**.

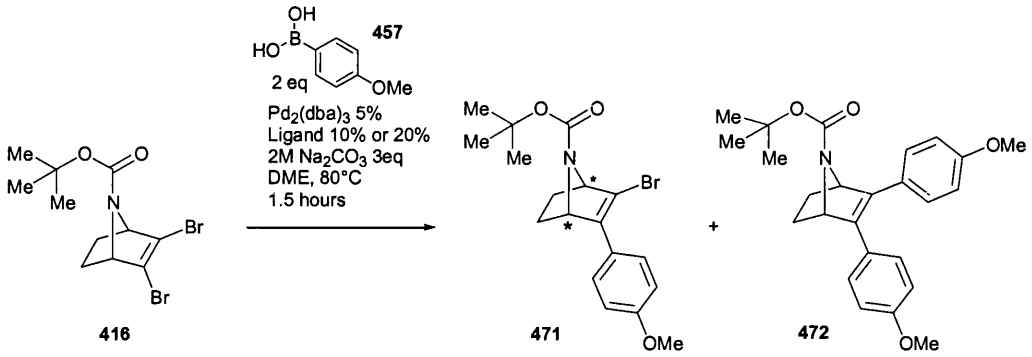


Scheme 95

Enantioselective reactions of dibromide **416**

In the final stages of the project it was felt that it was important to try an enantioselective coupling reaction. This was despite having failed to find successful reaction conditions at room temperature for either substrate, or conditions that allowed for the significant formation of *mono* products. The only set of conditions that were conducive for this study was the reaction of the BOC bromide **416** with 4-methoxy

benzene boronic acid **457** in DME (Scheme 92). This was the only reaction system that had formed enough mono adduct product to enable isolation and data collection. Conditions were found for the separation of **471** into its enantiomers *via* HPLC and then the reaction was screened on a 50mg scale (of dibromide **416**) and a 10% catalyst loading (Scheme 96). Twelve different chiral phosphine ligands were screened for reactivity and enantioselectivity. The results of the reaction are listed on Table 1.



Scheme 96

Ligand	Yield of **471**	ee of **471**[a]	Yield of **472**
(*R*)-BINAP **440**	9%	6%(+)	21%
Sulphide (*R*)-BINAP **442**	20%	10%(+)	10%
(*R*)-DUPHOS **450**	11%	0%	10%
Sulphide (*R*)-DUPHOS **451**	13%	9%(+)	12%
(*R*)-Tol-BINAP **444**	15%	11%(+)	12%
Sulphide (*R*)-Tol-BINAP **445**	20%	24%(+)	14%
1 eq (*R*)-MOP **334**	17%	2%(-)	5%
2 eq (*R*)-MOP **334**	13%	0%	23%
(*R*)-QUINAP **474**[b]	15%	3%(-)	3%
(*S*)-^{i}Pr-PHOX **475**[b]	15%	0%	10%
(*R*)-PHANEPHOS **476**[b]	11%	27%(+)	23%
(*R*)-(*S*)-JOSIPHOS **477**[b]	11%	6%(+)	12%

a: configurations shown are relative and not measured rotations

b: ligands are shown in Figure 33

Table 1

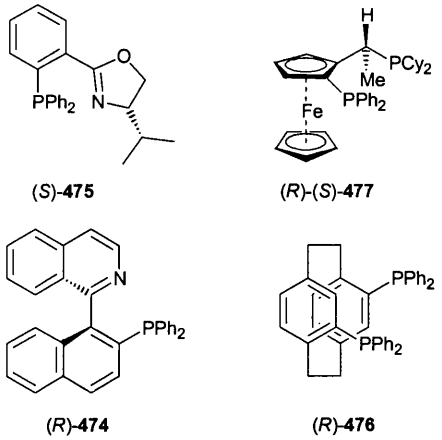
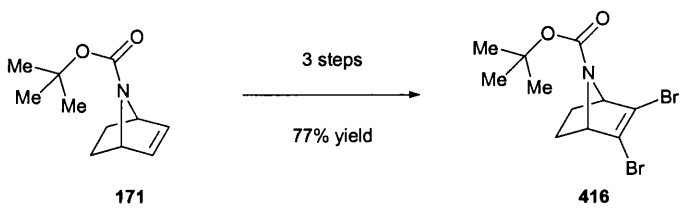


Figure 33

The greatest enantioselectivity was achieved using the PHANEPHOS ligand **476**. Most of the reactions show a general improvement in the ratio of *mono* to *bis* product obtained. The enantioselectivities demonstrated are too low for this to be consistent with a matched and mismatched effect (from an *in situ* kinetic resolution) and are possibly just to do with the increased steric bulk of these chiral catalyst systems in comparison with the racemic system of two equivalents of triphenyl phosphine. While none of the results are striking they show potential for improvement. Variations in solvent, temperature, boronic acid, base as well as palladium source have yet to be attempted and could yet yield a highly active and selective system. The novel sulphide ligands show increased efficacy over their non-sulphide analogues. The Tol-BINAP sulphide **445** in particular gave the best combination of yield and enantioselectivity of any of the ligands screened. This was a promising result although the ligands need to be tested in a more active reaction before any real conclusions can be made about their performance.

Conclusions

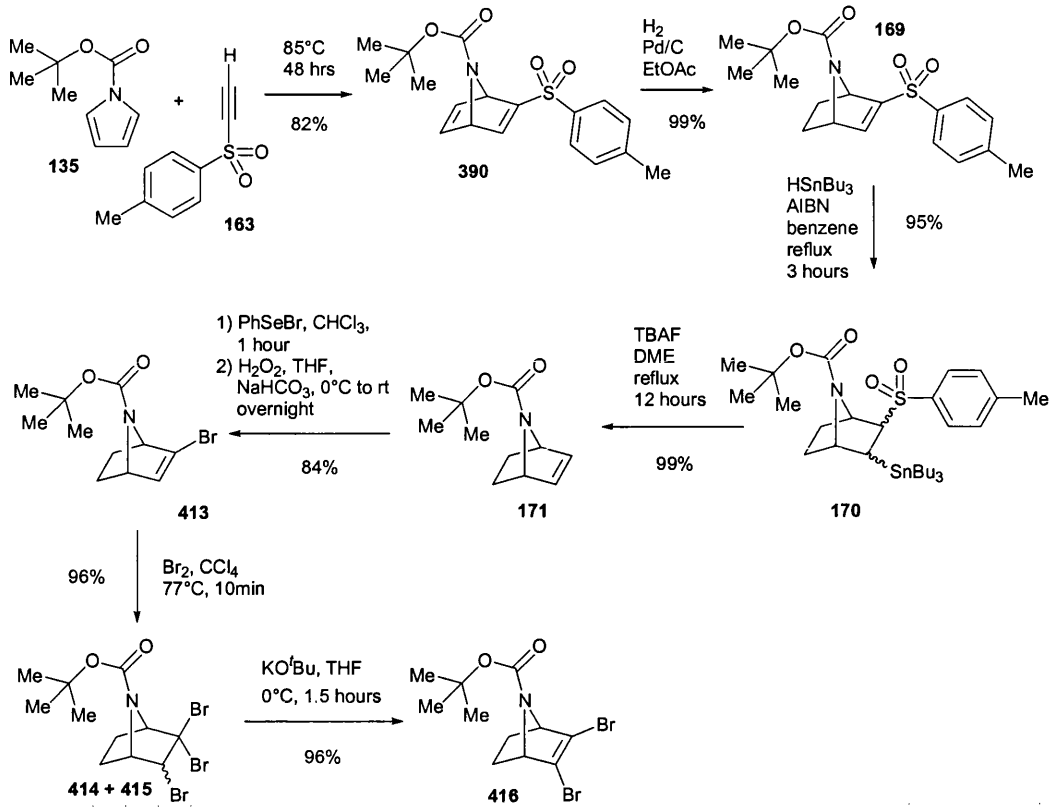
The preparation of aza bicyclic 1,2 vinyl halides has been accomplished, the intermediates needed for the proposed enantioselective synthesis of epibatidine. The synthetic pathway is high yielding and a range of different protecting group analogues can be prepared from the BOC derivative in high yields. Dibromide **416** can be prepared from known alkene **171** in three steps in an overall 77% yield (Scheme 97).



171 **416**

Scheme 97

The entire optimised synthetic pathway through to dibromide **416** from the commercially available BOC pyrrole **135** and tosyl acetylene **163** is detailed in Scheme 98. Dibromide **416** was prepared in an excellent overall 59% yield from acetylene **163**.



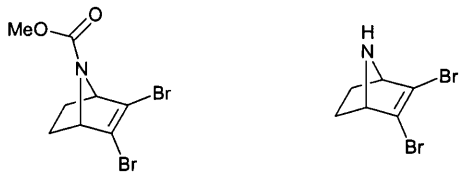
Scheme 98

The Suzuki-Miyaura coupling chemistry has yet to be fully explored. The work described on these substrates is only in its infancy. A much wider range of catalyst, base, boronic acid and solvent systems need to be examined to test their suitability and the scope of this reaction. The initial results obtained have been disappointing. The second addition or reaction is undoubtedly much faster than the first, leading in all racemic catalyst systems to a preponderance of the undesired *bis* adduct being formed. This is probably due to the electronic activating effect on the vinyl-bromide bond due to conjugation of the vinyl π-system into the newly coupled aryl system. The extent of the activation of the second halide to oxidative addition depends on the electronic nature of the aryl group. Electron poor aromatics activate the carbon-halide bond to a much greater degree than electron rich aryl systems. The enantiopure catalyst systems screened do relieve this effect to some extent. In particular the sulphide BINAP and Tol-BINAP ligands, **442** and **445**, seem to provide a good ratio of *mono* to *bis* products whilst displaying some enantioselectivity. More studies are needed to ascertain whether this reaction will become a synthetically useful process.

Further work

The results obtained to date in the coupling chemistry of dibromides **409** and **416** are preliminary, due to time constraints. A great many more conditions need to be tried and evaluated before any certain conclusions can be drawn on this methodology.

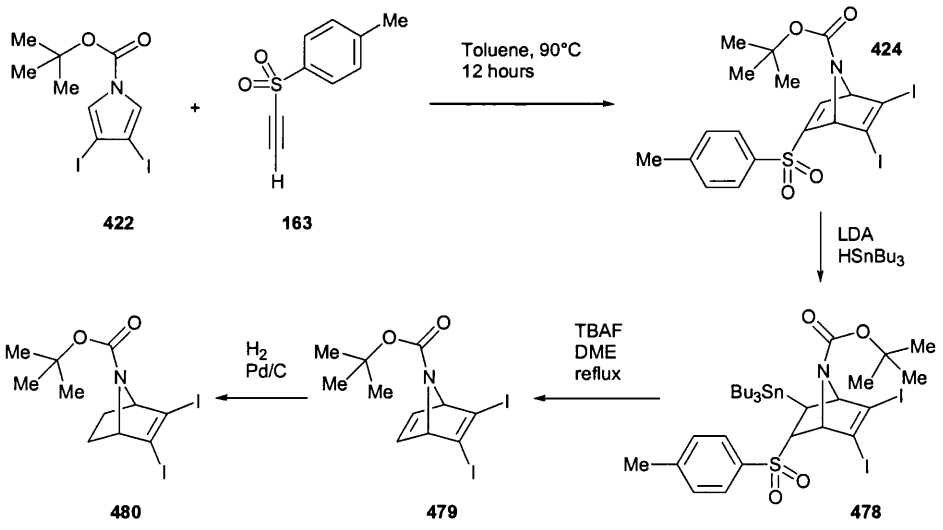
Given the increase in activity when moving from the tosyl protected amine **409** to the BOC protected amine **416**, the methyl carbamate protected **402** and free amine **417** derivatives became very interesting substrates to test (Figure 34). They are both less hindered substrates and potentially could offer an increase in reactivity over the first two dibromides prepared. Both were successfully synthesised but unfortunately there was no time remaining to test them with any Suzuki-Miyaura coupling chemistry.



402 **417**

Figure 34

The iodine analogues of all of the bromide substrates are still of interest despite the failure of diester **423** to react under the standard conditions. All of the diiodide analogues should be available *via* BOC diiodo pyrrole **422** reacting with acetylene sulphone **163** (Scheme 99). The use of alternative, conjugate addition methodology reported by Kaufmann *et al.* to prepare the stannyl-sulphone structure is required for this substrate.[21] The use of the AIBN/$HSnBu_3$ or LDA/TMSCl and hydrogenation strategies would be impossible due to the sensitivity of the vinyl iodides to reduction under radical conditions or the control over the hydrogenation reaction.



422 **163** **424** **478** **479** **480**

Scheme 99

From diiodide **480** all of the different protecting group derivatives that may be necessary for good selectivity can be prepared relatively simply.

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Experimental

General Experimental

All reactions were performed under an inert atmosphere of nitrogen or argon, in oven or flame dried glassware unless otherwise stated. Nitrogen was passed through a Drierite™ filled drying tube before use.

The solvents used in the reactions were distilled prior to use from the relevant drying agent. Toluene and hexane were distilled from sodium metal, ether and THF from sodium benzophenone ketyl. DCM and acetonitrile were distilled from calcium hydride. When used as a reaction solvent, EtOAc was purified and dried by filtration through a column of sodium sulphate prior to use. Petrol refers to the fraction of petroleum ether bp 40-60°C and was used without distillation.

Degassing, when required, was carried out by passing a fine stream of nitrogen or argon through the solvent at room temperature for at least 45 mins before use.

Flash chromatography was carried out using Merck Kieselgel 60H silica and Fisher Matrex Silica 60 silica. TLC was performed using Merck Kieselgel G/UV_{254} coated glass, aluminium and plastic plates. TLC plates were visualised using uv light at 254 nm and/or staining with $KMnO_4$ or vanillin dips.

Melting points were measured on a Buchi 535 melting point apparatus and are uncorrected.

IR spectra measurements were carried out as thin or liquid films on NaCl discs recorded on a Perkin Elmer FTIR 1600 spectrometer. The spectra are recorded in wave numbers (cm^{-1}) and were internally referenced.

Mass Spectra were carried out on a Finnigan MAT 8340 instrument at the University of Bath and by the EPSRC mass spectrometry service, Swansea.

Elemental analysis was performed on a Carbo Erba Stamentazione EA1506 analyser in the Chemistry department at the University of Bath.

^1H NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on a JEOL GX270 MHz, JEOL GX400 MHz or Bruker 360 and 300 MHz instrument's. Chemical shifts are reported in ppm from tetramethyl silane (δ_H = 0 ppm) or residual $CHCl_3$ (δ_H = 7.26 ppm) as an internal reference. Coupling constants are measured in Hertz. ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on the same instruments at 100 MHz, 90.5 MHz and 75.5 MHz respectively. $CDCl_3$ resonance (δ_C = t, 77.0 ppm) used as an internal reference.

All structural assignments of both protons and carbons were achieved with the aid of COSY, HMQC, DEPT and PENDANT experiments wherever possible and with comparisons from analagous literature compounds.

Protons that have chemical not magnetic equivalence (AA'BB' systems), as in the case of 1,4 substituted aromatics, are treated either as multiplets or as doublets, depending on their appearance in the spectra.

The additional signals due to nitrogen rotamers are included where they occur, in both ^{1}H and ^{13}C spectra.

An explanation for the proton and carbon assignments for the bicyclic compounds described in this thesis are are shown in Figure 1.

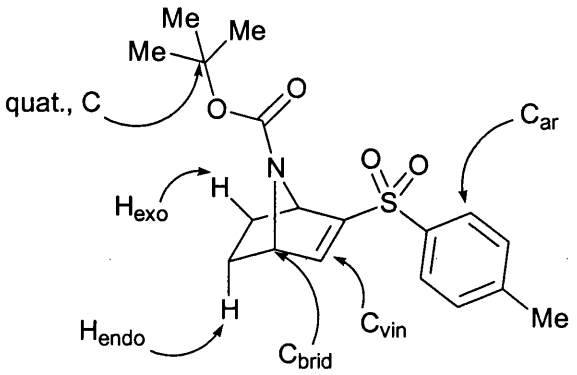


Figure 1

Optical rotations were performed on an Optical Activity LTD: AA-10 automatic polarimeter.

High performance liquid chromatography was carried out using a SP Thermo Separation products spectra SERIES and Spectra Physics Systems using Chiralcel OD® and AD® columns obtained from Fisher Scientific Supplies

All chemicals were bought from Acros, Aldrich, Avocado, Fluka, Lancaster or Strem chemical companies and were used without additional purification unless otherwise stated.

Ethynyl sulphone[1, 2], 3,4 diiodo pyrrole,[3] 2-bromo norbornene,[4, 5] 2,3 diiodo norbornene,[6] dipotassium azadicarboxylate,[7] 7-aza-bicyclo[2.2.1]heptane-2,3,7-tricarboxylic acid tert-butyl ester dimethyl ester,[8] were prepared as described in the literature.

Preparation of norbornene substrates

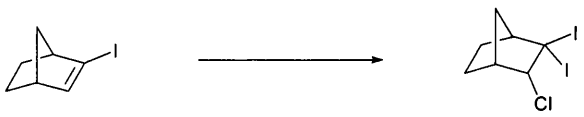
Preparation of bicyclo[2.2.1]heptane iodides

2-Iodo-bicyclo[2.2.1]hept-2-ene 371[9]

370 371

KO^{t}Bu (1.60 g, 14.2 mmol) was added to a stirred solution of diiodide **370** (4.5 g, 12.9 mmol) in THF (60 mL) at 0°C. A white ppt. immediately began to drop out of solution. The reaction was allowed to warm to room temperature and stirred for a further hour. EtOAc (150 mL) was added and the reaction mixture was washed with water (3 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (petrol) to yield vinyl iodide **371** (1.79 g, 49%) as a pale pink liquid; R_f (petrol) 0.71; ν_{max} (film) 1561 (C=C); δ_H (270 MHz) 6.35 (1H, d, J = 3.1, C_{vin}-H), 2.95 (1H, s, C_{vin}(I)-C_{brid}-H), 2.79 (1H, app. d, J = 1.5, C_{vin}(H)-C_{brid}-***H***), 1.65-1.50 (3H, m, ***H***-C(H)-C(H)-***H*** + C(H)-***H***), 1.15-1.10 (3H, m, ***H***-C(H)-C(H)-***H*** + C(H)-***H***); δ_C (100 MHz) 143.8 (C_{vin}-H), 96.4 (quat., C_{vin}-I), 53.3 (C_{brid}-H), 48.0 (C_{brid}-CH_2-C_{brid}), 44.7 (C_{brid}-H), 25.7 (CH_2), 24.1 (CH_2); *m/z* (CI) 221.0 (65%, (M+H)), 126.9 (I^+), 93.1 ((M+H) - I).

3-Chloro-2,2-diiodo-bicyclo[2.2.1]heptane 379

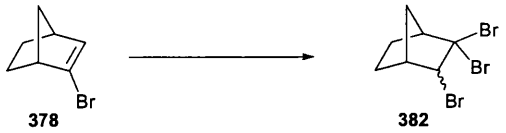


371 379

Iodine monochloride (176 mg, 1.086 mmol) was added to a solution of vinyl iodide **371** (200 mg, 0.905 mmol) in $CHCl_3$ (10 mL). The dark purple reaction mixture was then refluxed for 6 hours before cooling to room temperature and quenching with $Na_2S_2O_3$ (10% solution, 5 mL) to produce a colourless solution. The aqueous layer was removed and the organic layer was washed with water (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol to 20:1, petrol:EtOAc) to yield geminal *diiodide* **379** (345 mg, 63%) as a colourless solid; Mp 98-99°C; R_f (petrol) 0.19; δ_H (270 MHz) 4.09-4.01 (2H, m, 2 x C_{brid}-H), 2.85-2.75 (1H, m, C(Cl)-H_{exo}), 2.52-2.35 (2H, m), 2.29-2.21 (1H, m), 2.00-1.90 (1H, m), 1.86-1.73 (1H, m), 1.52-1.42 (1H, m); δ_C (100 MHz) 66.1 (C(H)Cl), 49.1 (quat., CI_2), 44.1 (C_{brid}-H), 42.5 (CH_2), 41.6 (CH_2), 39.4 (C_{brid}-H), 29.1 (CH_2); *m/z* (CI) 383.8/381.8 (100%, (M+)), 256.9/254.9 ((M+) - I), 127.0 (I+); Found (FAB+) 381.8482; $C_7H_9I_2{}^{35}Cl$ (M+), requires 381.84823.

Preparation of norbornene bromides

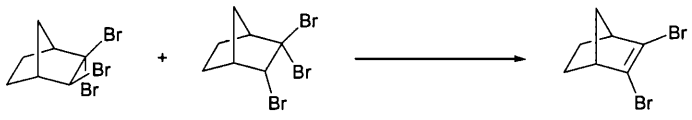
2,2,3-tribromonorbornane 382[10]



378 **382**

Bromine (23.36 g, 0.146 mol) in hot CCl_4 (250 mL) was added dropwise to a solution of 2-bromonorbornene **378**[4, 5] (23 g, 0.133 mol) in CCl_4 (500 mL) at 77°C. The bromine solution was kept warm through the use of a heat gun during the dropwise addition (~50 min). The reaction mixture was heated for a further 15 min after the addition of bromine was complete. The reaction mixture was then cooled to room temperature and washed with $Na_2S_2O_3$ (10% solution, 100 mL) and water (2 x 100 mL). The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo* to yield a crude yellow oil. The oil was dissolved in petrol (150 mL) and filtered through a pad of silica. After further washings with petrol (3 x 100 mL), the filtrate was concentrated *in vacuo* to yield tribromide **382** (42.5 g, 96%) as a colourless oil. ^{1}H NMR spectroscopy showed the material to be ~95% clean and a 3:7 mixture of the *endo:exo* isomers; δ_H (360 MHz) 5.14-5.13 (0.3H, m, C(Br)-H_{exo}), 4.47 (0.7H, d, J = 2.1, C(Br)-H_{endo}), 3.11 (0.7H, s, CBr_2-C_{brid}-H), 3.03 (0.3H, d, J = 3.6, CBr_2-C_{brid}-H), 2.51 (0.7H, d, J = 2.4, C(H)Br-C_{brid}-***H***), 2.46 (0.3H, br s, C(H)Br-C_{brid}-***H***), 2.37 (0.7H, dd, J = 11.0 and 1.1), 2.29 (0.3H, dd, J = 10.9 and 0.9), 2.11 (0.7H, dt, J = 12.7 and 2.3) 2.06-2.01 (0.3H, m), 1.87-1.80 (0.3H, m), 1.75-1.37 (4.7H, m).

2,3-Dibromo-bicyclo[2.2.1]hept-2-ene 380[10]



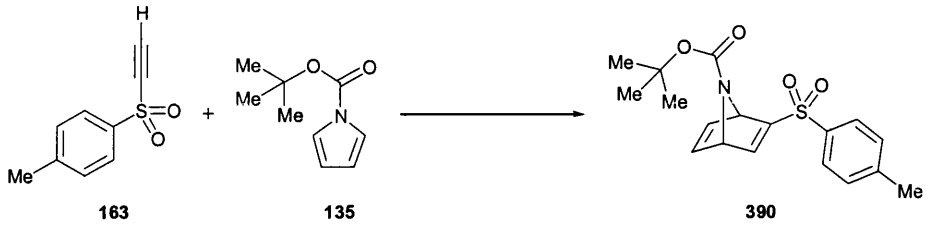
386 **385** **380**

Reaction carried out as dictated in the literature.[10] Product purified *via* vacuum distillation (27°C at 1.1mbar, (lit. 58-60°C at 1.5mmHg)[10] to give dibromide **380** as a colourless oil; R_f (petrol) 0.91; ν_{max} (film) 1585 (C=C); δ_H (360 MHz) 2.99 (s, 2H, C_{brid}-H), 1.77 (m, 1H, C(H)-***H***), 1.70-1.68 (m, 2H, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.33-1.31 (m, 2H, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$), 1.23-1.21 (m, 1H, C(H)-***H***); δ_C (90.5 MHz) 125.6 (quat., 2 x C_{vin}), 51.6 (C_{brid}-CH_2-C_{brid}), 47.0 (2 x C_{brid}-H), 25.7 (2 x CH_2).

Preparation of azabicycles

Synthesis of vinyl sulphone ***169***

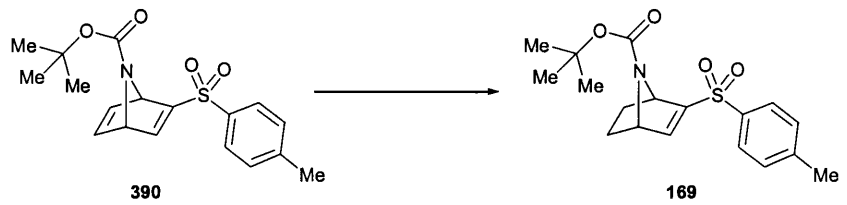
2-(Toluene-4-sulphonyl)-7-*tert*-butoxycarbonyl azabicyclo[2.2.1]hepta-2,5-diene 390[11]



163 **135** **390**

Freshly distilled BOC-pyrrole **135** (56.6 mL, 0.338 mol) was added to tosyl acetylene **163** (30.5 g, 0.169 mol) and the reaction mixture was heated to 83-85°C and stirred for 48 hours. The resultant black tar was then purified *via* flash chromatography (gradient elution, pure petrol (to remove excess pyrrole) to 3:1, petrol:EtOAc) to yield Diels-Alder adduct **390** (48.2 g, 82%), as a colourless crystalline solid; Mp 96-98°C (lit 97-98°C)[11, 12]; R_f (3:1, petrol:EtOAc) 0.32; ν_{max} (film) 1711 (C=O), 1594 (C=C), 1321 (SO_2), 1152 (SO_2); δ_H (360 MHz) 7.77 (2H, d, J = 8.2, SO_2C_{ar}-(C_{ar}-H)$_2$), 7.58 (H, s, C_{vin}-H), 7.36 (2H, d, J = 8.2, Me-C_{ar}-(C_{ar}-H)$_2$), 6.96 (1H, br s, C_{vin}-H), 6.89 (1H, dd, J = 5.3 and 2.5, SO_2-C_{vin}-C_{vin}-H), 5.39 (1H, br s, C_{brid}-H), 5.18 (1H, br s, C_{brid}-H), 2.45 (3H, s, C_{ar}-CH_3), 1.30 (9H, bs, C(CH_3)$_3$); δ_C (75.5 MHz) 158.9 (quat., C_{vin}-SO_2), 153.8 (quat., C=O), 152.5 (C_{vin}(H)-***C***$_{vin}$-H-(C_{brid})-C_{vin}(H)), 144.8 (quat., Me-C_{ar}), 143.8 (SO_2-C_{vin}-C_{brid}-***C***$_{vin}$-H), 142.9 (SO_2-C_{vin}-***C***$_{vin}$-H), 135.5 (quat., SO_2-C_{ar}), 129.9 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 128.0 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 81.3 (quat., C(Me)$_3$), 67.6 (C_{vin}(H)-***C***$_{brid}$-H), 66.8 (SO_2-C_{vin}-***C***$_{brid}$-H), 27.7 (C(***C***H$_3$)$_3$); *m/z* (FAB+) 348.1 (35%, (M+H)), 292.0 (100%, (M+H) - ^{t}Bu), 248.0 ((M+H) - $CO_2{}^t$Bu); Found (FAB+) 348.1269; $C_{18}H_{22}NO_4S$ (M+H), requires 348.1269.

2-(Toluene-4-sulphonyl)-7-*tert*-butoxycarbonyl azabicyclo[2.2.1]hept-2-ene 169[12]



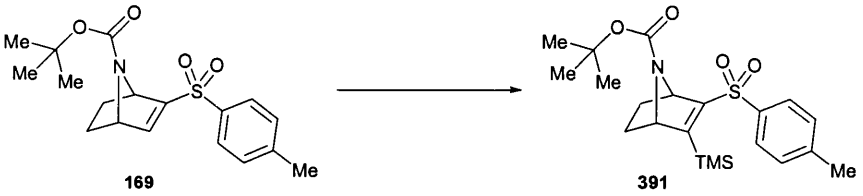
390 **169**

Pd/C (4.6 g, 10%/w Pd) was added to a solution of diene **390** (46.0 g, 132 mmol) in degassed EtOAc (600 mL) and stirred. The nitrogen atmosphere was then replaced with a hydrogen atmosphere at balloon pressure and the reaction was stirred for 48 hours. The hydrogen atmosphere was then removed and the reaction mixture was filtered through silica and the solvent was removed *in vacuo* to yield vinyl sulphone **169** (45.8 g, 99%) as pale yellow crystalline solid. Recrystallisation from absolute ethanol yields colourless crystalline material; Mp 147-148°C (EtOH) (lit 147-148°C)[12]; R_f (3:1, petrol:EtOAc) 0.37; ν_{max} (film) 1707 (C=O), 1594 (C=C), 1318 (SO_2), 1152 (SO_2); δ_H (300 MHz) 7.78 (2H, d, J = 8.1, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.34 (2H, d, J

= 8.1, Me-C_{ar}-(C_{ar}-H)$_2$), 7.03 (1H, d, J = 1.8, C_{vin}-H), 4.81 (1H, br s, C_{vin}(H)-C_{brid}-***H***), 4.74 (1H, d, J = 3.2, SO_2-C_{vin}-C_{brid}-H), 2.42 (3H, s, C_{ar}-CH_3), 2.05-1.91 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.39-1.28 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}), 1.24 (9H, br s, C(CH_3)$_3$); δ_C (75.5 MHz) 154.8 (quat., C=O), 148.7 (quat., C_{vin}-SO_2), 144.8 (quat., Me-C_{ar}), 144.1 (C_{vin}-H), 136.7 (quat., SO_2-C_{ar}), 130.0 (Me-C_{ar}-(C_{ar}-H)$_2$), 127.9 (SO_2-C_{ar}-(C_{ar}-H)$_2$), 80.7 (quat., C(Me)$_3$), 61.7 (C_{vin}(H)-C_{brid}-H), 60.8 (SO_2-C_{vin}-C_{brid}-H), 27.8 (C(CH_3)$_3$), 25.3 (CH_2), 24.1 (CH_2), 21.6 (C_{ar}-CH_3); Analysis calculated for $C_{18}H_{23}NO_4S$, C = 61.87%, H = 6.63%, N = 4.01%; Found C = 61.67%, H = 6.59%, N = 3.91%.

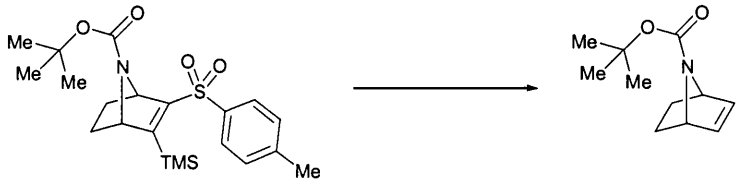
Cleavage of Sulphone via Kaufmann procedure

2-(Toluene-4-sulphonyl)-3-trimethylsilanyl-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 391[13]



BuLi (1.6M in hexanes, 5.25 mL, 8.4 mmol) was added dropwise to a solution of diisopropylamine (1.19 mL, 8.4 mmol) in THF (30 mL) at 0°C and the reaction was stirred for an additional 15 mins. The resulting LDA solution was then added dropwise to a solution of vinyl sulphone **169** (3.08 g, 8.0 mmol) in THF (150 mL) at -78°C, *via* a syringe, over 90 mins. The reaction mixture was stirred for an additional 2 hours before the anion was quenched at -78°C with the addition of freshly distilled TMSCl (1.11 mL, 8.8 mmol). The reaction was allowed to return to room temperature and stirred overnight. A saturated solution of ammonium chloride (150 mL) was added, followed by EtOAc (200 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 100 mL). The combined organic extract was treated with $NaHCO_3$ (10% solution, 100mL) and then dried (Na_2SO_4) and concentrated *in vacuo*. The solid residue was purified *via* flash chromatography (10:1, petrol:EtOAc) to yield vinyl silane **391** (2.48 g, 70%) as a colourless solid; Mp >250°C; R_f (5:1, petrol EtOAc) 0.83; ν_{max} (film) 1710 (C=O), 1317 (SO_2), 1152 (SO_2); δ_H (400 MHz) 8.00 (2H, d, J = 7.6, Me-C_{ar}-(C_{ar}-H)$_2$), 7.35 (2H, d, J = 7.6, SO_2C_{ar}-(C_{ar}-H)$_2$), 4.89 (1H, br s, C_{brid}-H), 4.69 (1H, d, J = 3.6, C_{brid}-H), 2.45 (3H, s, C_{ar}-CH_3), 2.04-1.88 (2H, m, 2 x C(H)-***H***), 1.60 (1H, br s, C(H)-***H***), 1.42-1.34 (1H, m, C(H)-***H***), 1.25 (9H, br s, C(CH_3)$_3$), 0.37 (9H, s, Si(CH_3)$_3$); δ_C (75.5 MHz) 161.3 (quat., br, C_{vin}), 154.9 (quat., C=O), 149.6 (quat., br, C_{vin}), 144.4 (quat., C_{ar}-Me), 137.3 (quat., C_{ar}-SO_2), 129.9 (Me-C_{ar}-(C_{ar}-H)$_2$), 127.8 (SO_2-C_{ar}-(C_{ar}-H)$_2$), 80.3 (quat., C(Me)$_3$), 66.7 (C_{brid}-H), 62.8 (C_{brid}-H), 27.7 (C(CH_3)$_3$), 25.0 (CH_2), 24.1 (CH_2), 21.6 (C_{ar}-CH_3), -0.1 (Si(CH_3)$_3$).

7-Aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 171[14, 15]

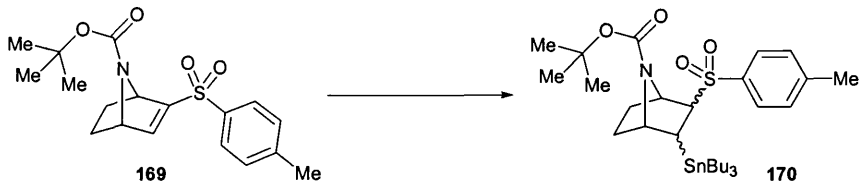


391 **171**

Freshly prepared dipotassium azodicarboxylate[7] (1.56 g, 8.04 mmol) was added to a stirred solution of vinyl silane **391** (1.13 g, 2.68 mmol) in MeOH (30 mL) at 0°C. The reduction was initiated by dropping in sufficient quantity of a 50% acetic acid solution to neutralise the solution (pH 6-7). The ice bath was then removed and the bright yellow suspension was stirred for 16 hours. After this time the yellow colour has disappeared and water (30 mL) was added and the reaction mixture was extracted with EtOAc (3 x 60 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was taken up in DCM (50 mL) and filtered through a pad of silica to yield reduced silane **392** (1.08 g, 95%) as a colourless solid; δ_H (400 MHz) 7.74 (2H, d, J = 8.0, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.35 (2H, d, J = 8.0, Me-C_{ar}-(C_{ar}-H)$_2$), 4.28 (1H, s, C_{brid}-H), 3.78-3.76 (1H, m, C_{brid}-H), 2.69-2.62 (1H, m, SO_2-C-H_{endo}), 2.45 (3H, s, C_{ar}-CH_3), 1.80-1.74 (2H, m, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.59-1.53 (2H, m, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$), 1.39 (9H, s, $C(CH_3)_3$), 1.25 (1H, br s, Si-C-H_{endo}) 0.31 (9H, s, $Si(CH_3)_3$). Silane **392** (1.02 g, 2.41 mmol) was then dissolved in a solution of TBAF (1 M in THF, 12.05 mL, 12.05 mmol) and stirred overnight for 16 hours at room temperature. EtOAc (40 mL) was then added and the reaction mixture was washed with water (3 x 10 mL) and the organic layer dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue filtered through a small pad of silica to provide the alkene **171** (400 mg, 86%) as a pale yellow liquid. This material was pure by ^{1}H NMR but the yellow colouring can be removed *via* careful flash chromatography (25:1, petrol:EtOAc); R_f (5:1, petrol:EtOAc) 0.75; ν_{max} (film) 1701 (C=O), 1597 (C=C); δ_H (300 MHz) 6.19 (2H, br s, 2 x C_{vin}-H), 4.62 (2H, br s, 2 x C_{brid}-H), 1-82-1.80 (2H, m, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.38 (9H, s, $C(CH_3)_3$), 1.07 (2H, d, J = 7.8, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$); δ_C (75.5 MHz) 154.9 (quat., C=O), 134.1 (2 x C_{vin}-H), 79.3 (quat., $C(Me)_3$), 59.4 (2 x C_{brid}-H), 28.0 ($C(\boldsymbol{C}H_3)_3$), 23.8 (2 x CH_2).

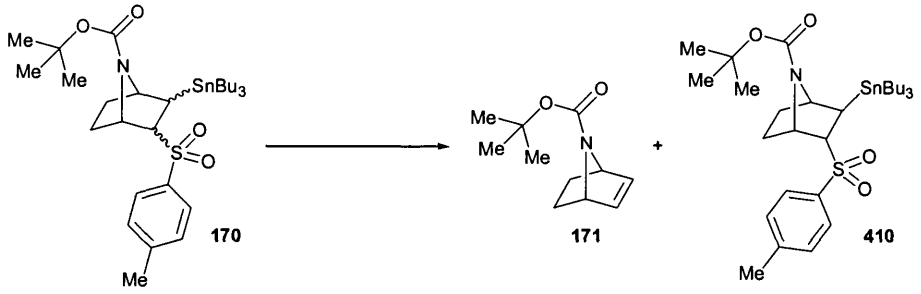
Cleavage of the sulphone via Carroll procedure

2-(Toluene-4-sulphonyl)-3-tributylstannyl-7-(*tert*-butoxy-carbonyl)-7-azabicyclo[2.2.1]heptane 170[14, 15]



Tributyltin hydride (8.33 g, 28.6 mmol) was added to solution of vinyl sulphone **169** (5 g, 14.3 mmol) and AIBN (150 mg) in benzene (250 mL). The reaction mixture was then heated to reflux for 3.5 hours. On cooling, silica (70 g) was added and the solvent was removed *in vacuo*. The resulting solid was purified *via* flash chromatography (gradient elution, petrol (to remove stannane residues) to 9:1, petrol:EtOAc) to yield stannyl-sulphone **170** (8.68 g, 95%) as a mixture of regioisomers, as a clear oil. On standing overnight at room temperature the oil solidified as a colourless waxy solid; Mp 45-55°C (lit 55-57°C)[15]; R_f (5:1, petrol:EtOAc) 0.65-0.73; ν_{max} (film) 1703 (C=O), 1318 (SO_2), 1147 (SO_2); δ_H (300 MHz) 7.71 (2H, br d, J = 8.0, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.33 (2H, br d, J = 8.0, Me-C_{ar}-(C_{ar}-H)$_2$), 4.24-4.19 (2H, m), 3.67-3.65 (1H, m), 2.63-2.56 (1H, m), 2.43 (3H, br s, C_{ar}-CH_3), 1.86-1.73 (1H, m), 1.72-1.61 (3H, m), 1.40 (9H, br s, $C(CH_3)_3$), 1.38-1.21 (12H, m), 0.86 (9H, br t, J = 7.1, 3 x CH_2CH_3), 0.70-0.60 (6H, m); *m/z* (FAB+) 640.4 (5%, (M+)), 584.4 ((M+) - ^{n}Bu), 528.2 (100%, (M+) - 2 x ^{n}Bu).

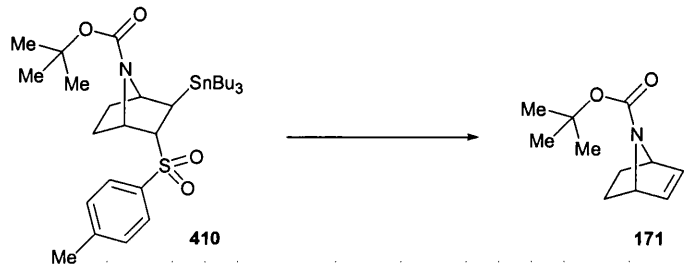
7-tert-Butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene 170[14, 15] and
2-*endo*-(Toluene-4-sulphonyl)-3-*exo*-tributylstannanyl-7-aza-bicyclo[2.2.1]heptane-7-carboxylic acid *tert*-butyl ester 410



TBAF (1M in THF, 33 mL, 33 mmol) was added to a stirred solution of stannyl-sulphone **170** (21 g, 32.8 mmol) in THF (70 mL) and the reaction was heated to reflux for 18 hours. The reaction mixture was then cooled to room temperature and the solvent removed *in vacuo*. Vaccuum distillation (40.5°C, 0.1 mmHg), gave alkene **171** (3.30 g, 52% (90% based on conversion)) as a colourless oil, data as before. The remaining residue was purified *via* flash chromatography (10:1 petrol:EtOAc) to yield stannane **410** (9.03 g) as a colourless waxy solid; Mp 56-58°C; R_f (5:1, petrol:EtOAc) 0.73; ν_{max} (film) 1704 (C=O), 1318 (SO_2), 1147 (SO_2); δ_H (300 MHz) 7.71 (2H, d, J = 8.1, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.32 (2H, d, J = 8.1, Me-C_{ar}-(C_{ar}-H)$_2$), 4.24 (1H, br

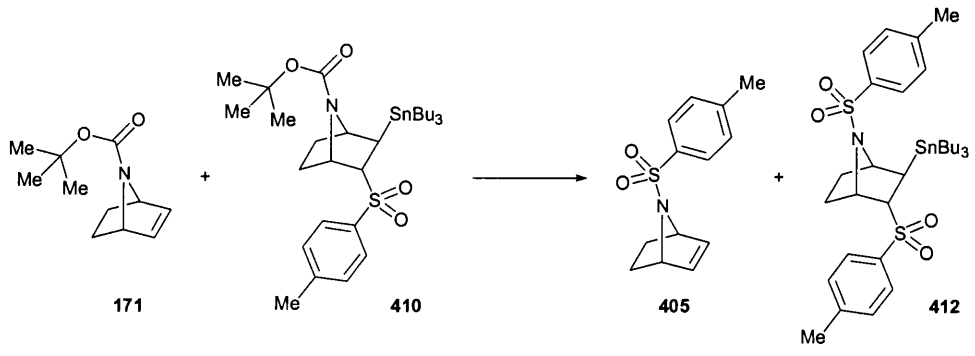
s, SO_2-C(H)-C_{brid}-***H***), 4.19 (1H, d, J = 3.6, Sn-C(H)-C_{brid}-***H***), 3.68-3.65 (1H, m, SO_2-C-H_{exo}), 2.62-2.56 (1H, m, C(H)-$\boldsymbol{H}_{endo}$), 2.42 (3H, s, C_{ar}-CH_3), 1.88-1.84 (1H, m, C(H)-$\boldsymbol{H}_{exo}$), 1.75-1.60 (2H, m, C(H)-$\boldsymbol{H}_{exo}$ + Sn-C-H_{endo}), 1.54-1.44 (1H, m, C(H)-$\boldsymbol{H}_{endo}$), 1.39 (9H, s, $C(CH_3)_3$), 1.39-1.21 (12H, m, 3 x C$\boldsymbol{H}_2$-CH_3 + 3 x CH_2-C$\boldsymbol{H}_2$-CH_2-), 0.86 (9H, t, J = 7.2, 3 x CH_2-C$\boldsymbol{H}_3$), 0.71-0.52 (6H, m, 3 x Sn-CH_2); δ_C (75.5 MHz) 154.1 (quat., C=O), 144.6 (quat., Me-C_{ar}), 137.2 (quat., SO_2-C_{ar}), 130.0 (Me-C_{ar}-(C_{ar}-H)$_2$), 127.9 (SO_2-C_{ar}-(C_{ar}-H)$_2$), 80.1 (quat., $C(Me)_3$), 69.5 (SO_2-C-H), 61.4 (Sn-C(H)-***C***$_{brid}$-H), 58.8 (SO_2-C(H)-***C***$_{brid}$-H), 29.2, 29.0, 28.9, 28.5, 28.1, 27.4, 21.5 (C_{ar}-***C***H_3), 13.6 (3 x -CH_2-***C***H_3), 8.5 (3 x Sn-CH_2-); *m/z* (FAB+) 640.2 (5%, (M+)), 584.1 ((M+) - ^{n}Bu), 528.1 (100%, (M+) - 2 x ^{n}Bu), 484.1 ((M+) - $CO_2{}^t$Bu, - ^{n}Bu), 430.1 ((M+) - $CO_2{}^t$Bu, - 2 x ^{n}Bu); Found (FAB+) 640.2568; $C_{30}H_{51}NO_4S^{119}Sn$ (M+H) requires 640.2572.

7-Aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 171[14, 15]



TBAF (1 M in THF, 52 mL, 52.2 mmol) was added to a stirring solution of stannyl sulphone **410** (6.686 g 10.4 mmol) in DME (120 mL). The reaction mixture was heated to reflux overnight (oil bath temperature 100°C). The solution was then allowed to cool to room temperature and EtOAc (200 mL) was added. The solution was washed with water (2 x 50 mL) and the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified *via* flash chromatography (15:1 petrol:EtOAc) to yield alkene **171** (2.01 g, 99%) as a colourless oil, data as above.

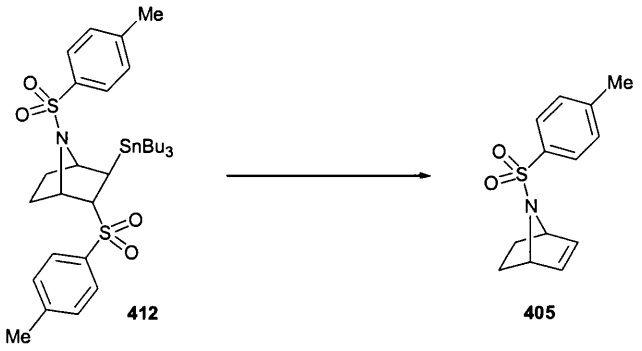
7-(Toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 405[16] **and**
2-*endo*,7-*Bis*-(toluene-4-sulphonyl)-3-*exo*-tributylstannanyl-7-aza-bicyclo[2.2.1]heptane 412



TFA (1.16 mL, 15.1 mmol) was added to a mixture (3 g) of alkene **171** (0.81 g, 4.15 mmol) and stannane **410** (2.189 g, 3.42 mmol) (a 6:5 ratio by ^{1}H NMR) and anisole (2.47 mL, 22.7 mmol) in DCM (10 mL). The

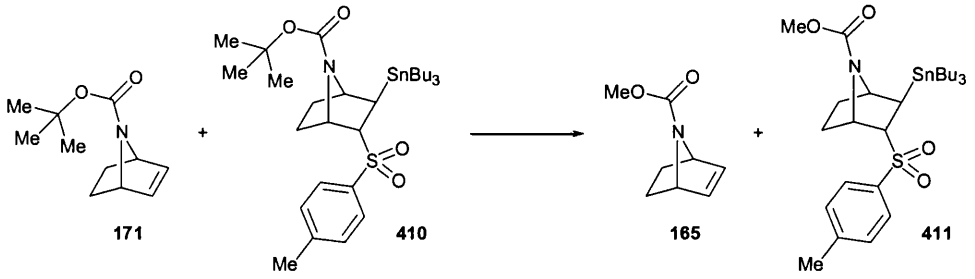
reaction was stirred at room temperature for two hours before the reacton mixture was concentrated *in vacuo*. The solid residue was dissolved in THF (30 mL) and cooled to 0°C. Pyridine (3.67 mL, 45.4 mmol) was added dropwise over 5 minutes followed by TsCl (2.88 g, 15.1 mmol). The reaction was allowed to return to room temperature and stir overnight. EtOAc (60 mL) was added and the reaction mixture was washed with water (2 x 20 mL) and brine (1 x 30 mL) before being dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, 20:1 to 5:1, petrol:EtOAc) to yield in order of elution; *stannane* **412** (1.88 g, 79%) as a colourless crystalline solid; Mp 86-88°C; R_f (5:1, petrol:EtOAc) 0.42; ν_{max} (film) 1347 (SO_2), 1321 (SO_2), 1159 (SO_2), 1148 (SO_2); δ_H (300 MHz) 7.73-7.69 (4H, m, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.35 (2H, d, J = 8.0, Me-C_{ar}-(C_{ar}-H)$_2$), 7.26 (2H, d, J = 8.0, Me-C_{ar}-C_{ar}-***H***), 4.28 (1H, app. t, J = 3.9, SO_2-C(H)-C_{brid}-***H***), 4.15 (1H, d, J = 4.3, Sn-C-C_{brid}-H), 3.72-3.68 (1H, m, SO_2-C-H_{exo}), 2.66-2.58 (1H, m, SO_2-C-C_{brid}-C(H)-***H***$_{endo}$), 2.44 (3H, s, C_{ar}-CH_3), 2.40 (3H, s, C_{ar}-CH_3), 2.00-1.92 (1H, m, Sn-C-C_{brid}-C(H)-***H***$_{exo}$), 1.77-1.67 (2H, m, Sn-C-C_{brid}-C(H)-***H***$_{endo}$ and SO_2-C-C_{brid}-C(H)-***H***$_{exo}$), 1.63 (1H, d, J = 6.6, Sn-C-H_{endo}) 1.40-1.16 (12H, m, CH_2-(C***H***$_2$-C***H***$_2$)$_3$-Me), 0.86 (9H, t, J = 7.0, -(CH_2-C***H***$_3$)$_3$), 0.69-0.49 (6H, m, Sn-(CH_2-)$_3$); δ_C (75.5 MHz) 144.9 (quat., Me-C_{ar}), 143.9 (quat., Me-C_{ar}), 137.2 (quat., SO_2-C_{ar}), 136.9 (quat., SO_2-C_{ar}), 130.1 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 129.6 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 128.0 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 127.6 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 69.7 (C(H)-SO_2), 64.5 (Sn-C-***C***$_{brid}$-H), 62.0 (SO_2-C-***C***$_{brid}$-H), 32.9 (SO_2-C-C_{brid}-***C***H_2), 29.4 (Sn-C-H), 28.8 (3 x Sn-CH_2-***C***H_2-), 27.3 (3 x -***C***H_2-CH_3), 25.1 (Sn-C-C_{brid}-***C***H_2), 21.6 (C_{ar}-***C***H_3), 21.5 (C_{ar}-***C***H_3), 13.6 (3 x -CH_2-***C***H_3), 8.6 (3 x Sn-***C***H_2-CH_2-); *m/z* (FAB+) 696.1 (10%, (M+H)), 638.0 (100%, (M+) - ^{n}Bu), 540.1 ((M+H) - tosyl); Found (ES+) 696.2199; $C_{32}H_{50}NO_4S_2Sn$ (M+H), requires 696.2203. X-ray crystal structure and data for stannane **412** can be found in Appendix E. And alkene **405** (783 mg, 76%) as a colourless crystalline solid; Mp 91-92°C (lit. 91.5-92°C)[16]; R_f (5:1, petrol:EtOAc) 0.35; ν_{max} (film) 1596 (C=C), 1337 (SO_2), , 1155 (SO_2); δ_H (300 MHz) 7.56 (2H, d, J = 8.2, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.22 (2H, d, J = 8.2, Me-C_{ar}-(C_{ar}-H)$_2$), 5.71 (2H, app. t, J = 1.2, 2 x C_{vin}-H), 4.58 (2H, app. dd, J = 1.8 and 1.2, 2 x C_{brid}-H), 2.38 (3H, s, C_{ar}-CH_3), 2.02-1.97 (2H, m, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.08-1.03 (2H, m, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$); δ_C (75.5 MHz) 144.9 (quat., Me-C_{ar}), 138.0 (quat., SO_2-C_{ar}), 132.5 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 129.9 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 126.5 (2 x C_{vin}-H), 62.3 (2 x C_{brid}-H), 25.2 (2 x CH_2), 21.9 (C_{ar}-CH_3); *m/z* (CI+) 250.0 (30%, (M+H)), 221.0 (100%, (M+) - CH_2=CH_2), 154.9 (tosyl+), 91.0 (tolyl+); Found (ES+) 250.0897; $C_{13}H_{16}NO_2S$ (M+H), requires 250.0902; Analysis for $C_{13}H_{15}NO_2S$ requires, C = 62.6%, H = 6.06%, N = 5.62%; Found C = 62.4%, H = 6.09%, N = 5.62%. X-ray crystal structure and data for alkene **405** can be found in Appendix C.

7-(Toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 405[16]



TBAF (1M in THF, 2.59 mL, 2.59 mmol) was added to a stirring solution of stannyl sulphone **412** (360 mg, 0.518 mmol) in DME (25 mL). The reaction mixture was then heated to reflux overnight (oil bath temperature 100°C). The solution was then allowed to cool to room temperature and EtOAc (40 mL) was added. The solution was washed with water (2 x 10 mL) and the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified *via* flash chromatography (5:1, petrol:EtOAc) to yield alkene **405** (122 mg, 95%) as a colourless crystalline solid, data as above.

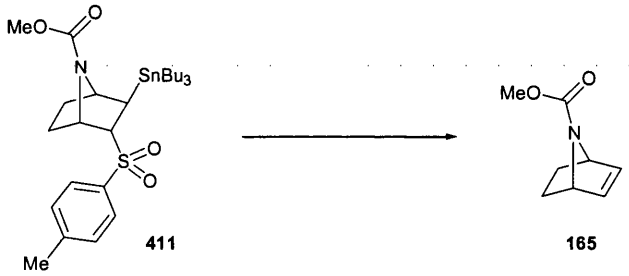
7-Aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid methyl ester 165[2] and 2-*endo*-(Toluene-4-sulphonyl)-3-*exo*-tributylstannanyl-7-aza-bicyclo[2.2.1]heptane-7-carboxylic acid methyl ester 411



TFA (1.16 mL, 15.1 mmol) was added to a mixture (3g) of alkene **171** (0.81 g, 4.15 mmol) and stannane **410** (2.189 g, 3.42 mmol) (a 6:5 ratio by NMR) and anisole (2.47 mL, 22.7 mmol) in DCM (10 mL). The reaction was stirred at room temperature for two hours before the reaction mixture was concentrated *in vacuo*. The solid residue was dissolved in THF (30 mL) and cooled to 0°C. Pyridine (3.67 mL, 45.4 mmol) was added dropwise over 5 minutes followed by methyl chloroformate (1.17 mL, 15.1 mmol). The reaction was allowed to return to room temperature and stir overnight. EtOAc (60 mL) was added and the reaction mixture was washed with water (2 x 20 mL) and brine (1 x 30 mL) before being dried (Na_2SO_4). Concentration *in vacuo* produced a brown oil. Vacuum distillation (40°C, 0.15 mmHg) afforded alkene **165** (438 mg, 69%) as a colourless oil; R_f (5:1, petrol:EtOAc) 0.51; ν_{max} (film) 1714 (C=O); δ_H (300 MHz) 6.16 (2H, s, 2 x C_{vin}-H), 4.65 (2H, s, 2 x C_{brid}-H), 3.55 (3H, s, CH_3), 1.78 (2H, d, J = 8.5, H_{exo}-C(H)-C(H)-H_{exo}), 1.05 (2H,

d, J = 8.5, $\boldsymbol{H}_{endo}$-C(H)-C(H)-$\boldsymbol{H}_{endo}$); δ_C (75.5 MHz) 155.6 (quat., C=O), 134.4 (2 x C_{vin}-H), 59.2 (2 x C_{brid}-H), 52.1 (CH_3), 23.5 (2 x CH_2). The remaining residue was purified *via* flash chromatography (10:1, petrol:EtOAc) to yield *stannane* **411** (1.52 g, 74%) as a colourless viscous liquid; R_f (5:1, petrol:EtOAc) 0.51; ν_{max} (film) 1714 (C=O), 1319 (SO_2), 1147 (SO_2); δ_H (300 MHz) 7.71 (2H, d, J = 8.1, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.33 (2H, d, J = 8.1, Me-C_{ar}-(C_{ar}-H)$_2$), 4.28-4.27 (2H, m, 2 x C_{brid}-H), 3.68-3.65 (1H, m, SO_2-C-H), 3.61 (3H, s, OCH_3), 2.64-2.57 (1H, m, C(H)-$\boldsymbol{H}_{endo}$), 2.42 (3H, s, C_{ar}-CH_3), 1.89-1.76 (1H, m, C(H)-$\boldsymbol{H}_{exo}$), 1.75-1.60 (3H, m, C(H)-$\boldsymbol{H}_{exo}$ + C(H)-$\boldsymbol{H}_{endo}$ + Sn-C-H), 1.44-1.31 (6H, m, 3 x Sn-CH_2-C$\boldsymbol{H}_2$-), 1.29-1.18 (6H, m, 3 x (C$\boldsymbol{H}_2$-CH_3)), 0.85 (9H, t, J = 5.8, 3 x (CH_2-C$\boldsymbol{H}_3$)), 0.73-0.64 (6H, m, 3 x Sn-CH_2-); δ_C (75.5 MHz) 154.9 (quat., C=O), 144.7 (quat., Me-C_{ar}), 137.1 (quat., SO_2-C_{ar}), 130.0 (Me-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 127.9 (SO_2-C_{ar}-(C_{ar}-H)$_2$), 69.4 (SO_2-C-H), 59.2 (C_{brid}-H), 58.9 (C_{brid}-H), 52.4 ($CO_2\boldsymbol{C}H_3$), 35.1 (C_{brid}-$\boldsymbol{C}H_2$), 28.8 (3 x Sn-CH_2-$\boldsymbol{C}H_2$-), 28.7 (Sn-C-H), 26.9 (3 x -CH_2-$\boldsymbol{C}H_2$-CH_3), 24.6 (C_{brid}-$\boldsymbol{C}H_2$), 21.5 (C_{ar}-$\boldsymbol{C}H_3$), 13.6 (3 x -CH_2-$\boldsymbol{C}H_3$), 6.5 (3 x Sn-CH_2-); *m/z* (CI+) 617.3 (20%, (M+NH_4)), 600.3 (M+H), 559.3 ((M+NH_4) - ^{n}Bu), 542.2 ((M+H) - ^{n}Bu), 444.3 ((M+H) - tosyl); Found (ES+) 600.2168; $C_{27}H_{46}NO_4SSn$ (M+H), requires 600.2169.

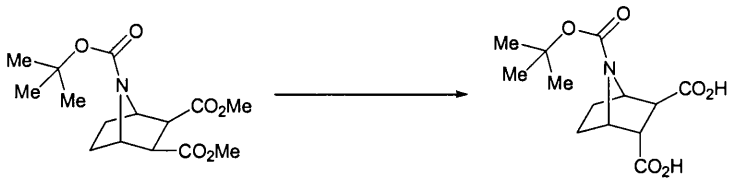
7-Aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid methyl ester 165[2]



TBAF (1 M in THF, 7.52 mL, 7.52 mmol) was added to stannane **411** (0.9 g, 1.5 mmol) in DME (20 mL) at room temperature. The reaction mixture was heated to reflux overnight before cooling. EtOAc (50 mL) was added and the reaction mixture washed with water (2 x 20 mL) before drying (Na_2SO_4) and concentrating *in vacuo*. The residue was purified *via* flash chromatography (10:1, petrol:EtOAc) to yield alkene **165** (214 mg, 93%) as a colourless oil, data as before.

Decarboxylation strategy

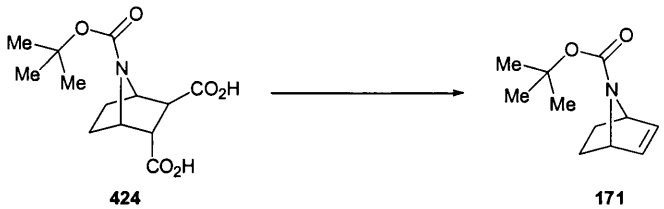
7-Aza-bicyclo[2.2.1]heptane-2,3,7-tricarboxylic acid 7-*tert*-butyl ester 424



426 **424**

NaOH (2 M, 24 mL, 47.9 mmol) was added to diester **426**[8] (3 g, 9.58 mmol) in THF (75 mL) and the reaction mixture was stirred overnight. Ether (100 mL) was then added as well as sufficient HCl (1M) to adjust pH to 4~5. The reaction mixture was then washed with dilute aqueous HCl (2 x 20 mL) and brine (1 x 25 mL) before drying (Na_2SO_4). The solvent was removed *in vacuo* and the residue was then recrystallised from MeCN to yield *diacid* **424** (2.54 g, 93%) as a colourless crystalline solid; Mp 155-157°C; ν_{max} (film) 3200 (O-H), 1736 (C=O), 1711 (C=O); δ_H (300 MHz, CD_3OD) 4.50 (1H, d, J = 4.8, CO_2-C(H_{endo})-C_{brid}-***H***), 4.43 (1H, app. t, J = 4.6, CO_2-C(H_{exo})-C_{brid}-***H***), 3.50-3.47 (1H, m, CO_2-C-H_{exo}), 2.94 (1H, d, J = 5.1, CO_2-C-H_{endo}), 1.88-1.81 (1H, m, CO_2-C(H_{endo})-C_{brid}(H)-C-***H***$_{exo}$), 1.75-1.71 (1H, m, CO_2-C(H_{exo})-C_{brid}(H)-C-***H***$_{exo}$), 1.61-1.51 (2H, m, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$), 1.42 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, CD_3OD) 175.8 (quat., HO(C=O)), 174.7 (quat., HO(C=O), 156.8 (quat., ^{t}BuO(C=O)), 82.2 (quat., $C(Me)_3$), 62.4 (CO_2-C(H_{endo})-***C***$_{brid}$-H), 59.8 (CO_2-C(H_{exo})-***C***$_{brid}$-H), 51.9 (CO_2-***C***-H_{endo}), 50.4 (CO_2-***C***-H_{exo}), 30.7 (CH_2), 28.8 (C(***C***$H_3)_3$), 26.1 (CH_2); *m/z* (CI+) 303.1 (30%, ($M+NH_4$)), 286.1 (30%, (M+H)), 247.0 (100%, ($M+NH_4$) - ^{t}Bu), 230.0 ((M+H) - ^{t}Bu), 203.0 (($M+NH_4$) - $CO_2{}^t$Bu), 185.9 ((M+H) - $CO_2{}^t$Bu), 141.9 ((M+H) - $CO_2{}^t$Bu, - CO_2); Found (ES+) 286.1291; $C_{13}H_{20}NO_6$ (M+H), requires 286.1290.

7-Aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 171[14, 15]



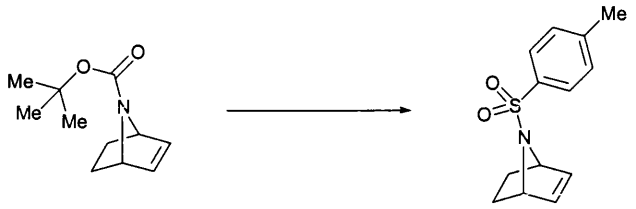
424 **171**

Diacid **424** (500 mg, 1.75 mmol) was suspended in benzene (5 mL) with LTA (0.932 g, 2.10 mmol) and pyridine (0.212 mL, 2.63 mmol). The suspension was then heated to reflux, during which time the suspension forms a yellow solution. The reaction mixture was heated at reflux for 3.5 hours. On cooling, EtOAc (30 mL) was added and the solution was washed with water (3 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (20:1, petrol:EtOAc) to yield alkene **171** (21 mg, 9%) as a colourless oil, data as before.

Preparation of azabicyclo[2.2.1]heptene dibromides

Tosyl protected analogue

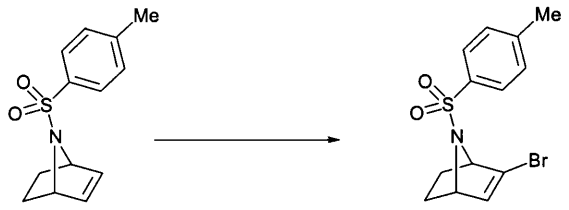
7-(Toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 405[16]



171 **405**

TFA (0.395 mL, 5.12 mmol) was added to a stirring solution of BOC alkene **171** (500 mg, 2.56 mmol) in DCM (5 mL) at room temperature. The reaction was stirred for two hours and the reaction mixture was then concentrated *in vacuo*. The residue was dissolved in THF (12 mL), cooled to 0°C and stirred. NEt_3 (1.43 mL, 10.24 mmol) was added dropwise, followed by TsCl (976 mg, 5.12 mmol) and the reaction mixture stirred overnight. The reaction mixture was then concentrated *in vacuo* and the residue was taken up in EtOAc (20 mL), washed with water (2 x 10 mL), then the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (10:1, petrol:EtOAc) to yield tosyl amine **405** (498 mg, 78%) as a colourless crystalline solid, data as above.

2-Bromo-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 406

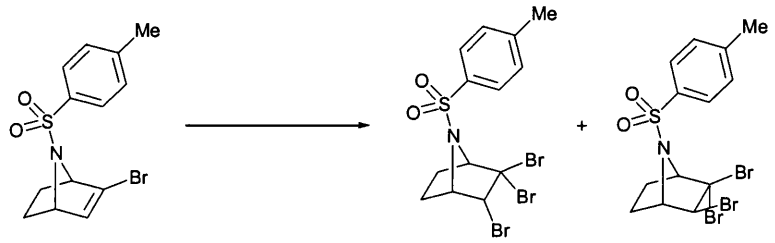


405 **406**

Phenyl selenium bromide (208 mg, 0.882 mmol) was added to a solution of alkene **405** (200 mg, 0.802 mmol) in $CHCl_3$ (20 mL). The reaction was stirred for two hours. The solvent was then removed *in vacuo* and the residue was dissolved in THF (15 mL) and cooled to 0°C. $NaHCO_3$ (101 mg, 1.2 mmol) was added followed by H_2O_2 (35% w/w solution in H_2O, 0.3 g, 3.01 mmol) and the reaction was allowed to return to room temperature and stir overnight. EtOAc (30 mL) was then added and the reaction mixture was washed with water (2 x 15 mL), the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient elution, petrol to 10:1, petrol:EtOAc) to give the *vinyl bromide* **406** (208 mg, 79% yield) as a colourless crystalline solid; Mp 114-115°C; R_f (5:1, petrol:EtOAc) 0.32; ν_{max} (film) 1340 (SO_2), 1154 (SO_2); δ_H (300 MHz) 7.64-7.60 (2H, m, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.29-7.27 (2H, m, Me-

C_{ar}-(C_{ar}-H)$_2$), 5.75-5.73 (1H, m, C_{vin}-H), 4.62-4.61 (1H, m, C_{vin}(H)-C_{brid}-***H***), 4.52 (1H, d, J = 3.3, C_{vin}(Br)-C_{brid}-H), 2.42 (3H, s, C_{ar}-CH_3), 2.14-2.01 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.32-1.21 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}); δ_C (75.5 MHz) 143.6 (quat., Me-C_{ar}), 135.7 (quat., SO_2-C_{ar}), 132.1 (C_{vin}-H), 129.8 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 128.4 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 123.0 (quat., C_{vin}-Br), 67.5 (C_{vin}(Br)-***C***$_{brid}$-H), 64.0 (C_{vin}(H)-***C***$_{brid}$-H), 26.4 (CH_2), 24.6 (CH_2), 21.5 (C_{ar}-CH_3); *m/z* (CI+) 346.9/344.9 (100%, (M+NH_4)), 329.9/327.9 (60%, (M+H)); 300.9/298.9 ((M+) - CH_2=CH_2), 267.0 ((M+NH_4) - Br), 249.9 ((M+) - Br); Found (FAB+) 345.0274; $C_{13}H_{18}{}^{79}BrN_2O_2S$, (M+$NH_4$), requires 345.0272; Analysis calculated for $C_{13}H_{14}Br_3NO_2S$, C = 47.6%, H = 4.30%, N = 4.27%; Found C = 47.6%, H = 4.34%, N = 4.30%.

2,2,3-*endo*-Tribromo-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]heptane 407 and 2,2,3-*exo*-Tribromo-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]heptane 408



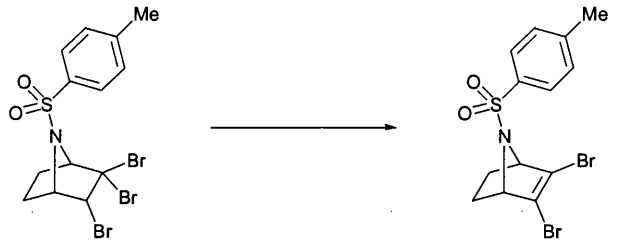
406 407 408

Bromine (54 mg, 0.335 mmol) in hot CCl_4 (3 mL) was added dropwise to a solution of vinyl bromide **406** (100 mg, 0.305 mmol) in CCl_4 (4 mL) at 77°C. The solution of bromine was kept warm during the addition with a heat gun. The reaction was stirred for a further 10 min after the complete addition of the bromine before the reaction mixture was cooled to room temperature. DCM (10 mL) and $Na_2S_2O_3$ (10% solution, 10 mL) were then added. The organic layer was separated and washed with $NaHCO_3$ (saturated solution, 2 x 10 mL) and water (2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol to 10:1, petrol:EtOAc) to give compounds in order of elution; *endo tribromide* **407** (79 mg, 53%) as a colourless crystalline solid; Mp 110-111°C; R_f (5:1, petrol:EtOAc) 0.61; ν_{max} (film) 1332 (SO_2), 1161 (SO_2); δ_H (300 MHz) 7.85 (2H, d, J = 8.2, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.32 (2H, d, J = 8.2, Me-C_{ar}-(C_{ar}-H)$_2$), 4.97 (1H, dd, J = 4.6 and 1.3, C(Br)-H_{exo}), 4.61 (1H, d, J = 4.7, CBr_2-C_{brid}-H), 4.25 (1H, app. t, J = 4.6, C(H)Br-C_{brid}-***H***), 2.44 (3H, s, C_{ar}-CH_3), 2.41-2.33 (1H, m, CBr_2-C_{brid}-C(H)-H_{endo}), 2.18-2.10 (1H, m, C(H)Br-C_{brid}-C(H)-H_{endo}), 2.04-1.84 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}); δ_C (75.5 MHz) 144.4 (quat., Me-C_{ar}), 136.3 (quat., SO_2-C_{ar}), 129.7 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 127.7 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 74.8 (CBr_2-***C***$_{brid}$-H), 65.6 (quat., CBr_2), 66.0 (CBr(H)-***C***$_{brid}$-H), 64.0 (C(Br)-H), 27.7 (CH_2), 23.5 (CH_2), 21.6 (C_{ar}-CH_3); *m/z* (CI+) 491.6/489.6/487.6/485.6 (30%, (M+H)), 409.7/407.7/405.7 (85%, (M+) - Br), 329.8/327.8 ((M+H) - 2 x Br), 300.8/298.8 ((M+) - 2 x Br, - CH_2=CH_2), 154.9 (100%, (tosyl+)), 91.0 (tolyl+); Found (FAB+) 487.8346; $C_{13}H_{15}{}^{79}Br_2{}^{81}BrNO_2S$ requires 487.8353; Analysis calculated for $C_{13}H_{14}Br_3NO_2S$, C = 32.0%, H = 2.89%, N = 2.87%; Found C = 32.1%, H = 2.89%, N = 2.89%. And *exo-tribromide* **408** (54 mg, 36%) as a colourless crystalline solid; Mp 143-144°C; R_f (5:1, petrol:EtOAc) 0.51; ν_{max} (film) 1597, 1447, 1403, 1323 (SO_2), 1155 (SO_2); δ_H (300 MHz) 7.89 (2H, d, J = 8.2, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.32 (2H, d, J = 8.2, Me-C_{ar}-(C_{ar}-

H)$_2$), 4.67-4.65 (1H, m, CBr_2-C_{brid}-H), 4.32 (1H, s, C(Br)-H_{endo}), 4.22-4.20 (1H, m, CBr(H)-C_{brid}-***H***), 2.57-2.50 (1H, m, (CH)-$\boldsymbol{H}_{endo}$), 2.44 (3H, s, C_{ar}-CH_3), 2.24-2.15 (2H, m, C(H)-$\boldsymbol{H}_{exo}$), 1.73-1.66 (1H, C(H)-$\boldsymbol{H}_{endo}$); δ_C (75.5 MHz) 144.3 (quat., Me-$\boldsymbol{C}_{ar}$), 136.1 (quat., SO_2-$\boldsymbol{C}_{ar}$), 129.5 (Me-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 127.9 (SO_2-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 75.4 (CBr_2-$\boldsymbol{C}_{brid}$-H), 70.1 (C(H)Br-$\boldsymbol{C}_{brid}$-H), 67.4 (quat., CBr_2), 64.8 (C(H)-Br), 29.1 (CH_2), 26.9 (CH_2), 21.6 (C_{ar}-$\boldsymbol{C}H_3$); *m/z* (CI+) 491.7/489.7/487.7/485.7 (45%, (M+H)), 409.8/407.8/405.8 (85%, (M+) - Br), 329.9/327.9 ((M+H) - 2 x Br), 300.8/298.8 ((M+) - 2 x Br, - CH_2=CH_2), 255.8/253.8/251.8 ((M+H) - Br, - tosyl), 154.9 (tosyl+), 91.0 (tolyl+); Found (FAB+) 487.8357; $C_{13}H_{15}{}^{79}Br_2{}^{81}BrNO_2S$ requires 487.8353; Analysis calculated for $C_{13}H_{14}Br_3NO_2S$, C = 31.99% H = 2.89%, N = 2.87%; Found C = 31.98%, H = 2.92%, N = 2.86%.

On a 3.4 gram scale a mixture of *endo* and *exo tribromides* **407** and **408** was achieved in a 96% yield.

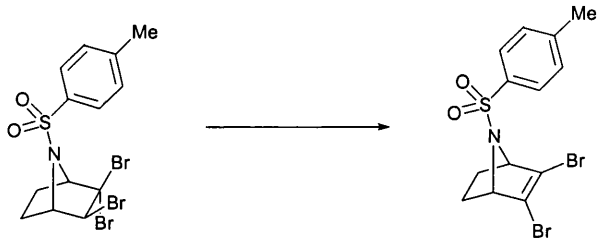
2,3-Dibromo-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 409



407 **409**

KO^{t}Bu (7.5 mg, 0.0624 mmol) was added to a stirring solution of tribromide **407** (30 mg, 0.0615 mmol) in 1 mL of THF at 0°C. The reaction was stirred for 20 mins before the ice bath was removed and the reaction was allowed to return to room temperature. The reaction was stirred for an additional 90 mins, in which time a white ppt. gradually forms. The reaction was filtered through a pad of silica and washed through with DCM (2 x 3 mL). The solvent was then concentrated *in vacuo* to yield vinyl dibromide **409** (24 mg, 96%) as a white crystalline solid; Mp 194-195°C; R_f (5:1, petrol:EtOAc) 0.41; ν_{max} (film) 1337 (SO_2), 1157 (SO_2); δ_H (300 MHz) 7.63 (2H, d, J = 8.2, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.30 (2H, d, J = 8.2, Me-C_{ar}-(C_{ar}-H)$_2$), 4.58-4.56 (2H, m, 2 x C_{brid}-H), 2.41 (3H, s, C_{ar}-CH_3), 2.12-2.08 (2H, m, $\boldsymbol{H}_{exo}$-C(H)-C(H)-$\boldsymbol{H}_{exo}$), 1.39-1.35 (2H, m, $\boldsymbol{H}_{endo}$-C(H)-C(H)-$\boldsymbol{H}_{endo}$); δ_C (75.5 MHz) 143.6 (quat., Me-C_{ar}), 135.0 (quat., SO_2-C_{ar}), 129.8 (Me-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 128.0 (SO_2-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 123.6 (2 x C_{vin}-Br), 68.6 (2 x C_{brid}-H), 26.0 (2 x CH_2), 21.4 (C_{ar}-CH_3); *m/z* (CI+) 427.0/425.0/423.0 (100%, (M+NH_4)), 409.9/407.9/405.9 (25%, (M+H)), 346.1/344.1 ((M+NH_4) - Br), 330.1/328.1 ((M+H) - Br), 267.1 ((M+NH_4) - 2 x Br), 250.1 ((M+H) - 2 x Br); Found (FAB+) 407.9089; $C_{13}H_{14}{}^{79}Br{}^{81}BrNO_2S$ (M+H), requires 407.9091; Analysis calculated for $C_{13}H_{14}Br_2NO_2S$, C = 38.35%, H = 3.22%, N = 3.44%; Found C = 38.33%, H = 3.24%, N = 3.37%. X-ray crystal structure and data for dibromide **409** can be found in Appendix D.

2,3-Dibromo-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 409



408 **409**

KO^{t}Bu (7.5 mg, 0.0624 mmol) was added to a stirring solution of tribromide **408** (30 mg, 0.0615 mmol) in THF (1 mL) at 0°C. The reaction was stirred for 20 mins before the ice bath was removed and the reaction was allowed to return to room temperature. The reaction was stirred for an additional 90 mins, in which time a white ppt. gradually forms. The reaction was filtered through a pad of silica and washed through with DCM (2 x 3 mL). The solvent was then concentrated *in vacuo* to yield vinyl dibromide **409** (24 mg, 96%) as a white crystalline solid, data as above.

On a 4.5gram scale (of a mixture of isomers **407** and **408**) the dibromide **409** was obtained in a 96% yield.

BOC protected analogue

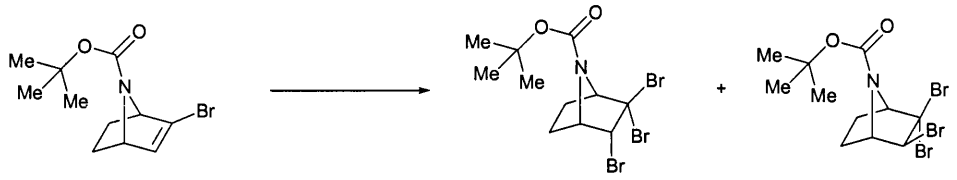
2-Bromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 413

171 **413**

Phenyl selenium bromide (823 mg, 3.49 mmol) was added to a solution of alkene **171** (650 mg, 3.32 mmol) in $CHCl_3$ (15 mL). The reaction was stirred for 2 hours, the solvent was then removed *in vacuo* and the residue was dissolved in THF (15 mL) and cooled to 0°C. $NaHCO_3$ (418 mg, 4.98 mmol) was added followed by H_2O_2 (35%w/w solution in H_2O, 1.61 g, 16.6 mmol) and the reaction was stirred overnight. EtOAc (30 mL) was then added and the reaction mixture was washed with water (2 x 15 mL), the organic layer dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol to 10:1, petrol:EtOAc) to give the *vinyl bromide* **413** (780 mg, 84%) as a colourless oil; R_f (5:1, petrol:EtOAc) 0.71; ν_{max} (film) 1701 (C=O), 1575 (C=C); δ_H (300 MHz) 6.23 (1H, br s, C_{vin}-H), 4.62 (1H, br s, C_{vin}(H)-C_{brid}-***H***), 4.52 (1H, br s, C_{vin}(Br)-C_{brid}-H), 1.92-1.80 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.39 (9H, s, $C(CH_3)_3$), 1.34-1.18 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}); δ_C (75.5 MHz) 154.8 (quat., C=O), 134.4 (C_{vin}-H), 123.9 (quat., C_{vin}-Br), 80.3 (quat., $C(Me)_3$), 65.8 (C_{vin}(Br)-C_{brid}-H), 61.9 (C_{vin}(H)-C_{brid}-H), 28.1 ($C(CH_3)_3$), 25.1 (CH_2), 23.9 (CH_2); *m/z* (CI+) 293.0/291.0 ($M+HH_4$) 275.9/273.9 (80%, (M+H)), 219.8/217.8

((M+H) - ^{t}Bu), 196.0 ((M+H) - Br), 193.0/191.0 ((M+NH_4) - $CO_2{}^t$Bu), 175.8/173.8 (100%, (M+H) - $CO_2{}^t$Bu), 96.0 ((M+H) - $CO_2{}^t$Bu, - Br); Found (ES+) 274.0438; $C_{11}H_{17}{}^{79}BrNO_2$ (M+H), requires 274.0442.

2,2,3-*endo*-Tribromo-7-aza-bicyclo[2.2.1]heptane-7-carboxylic acid *tert*-butyl ester 414 and 2,2,3-*exo*-Tribromo-7-aza-bicyclo[2.2.1]heptane-7-carboxylic acid *tert*-butyl ester 415

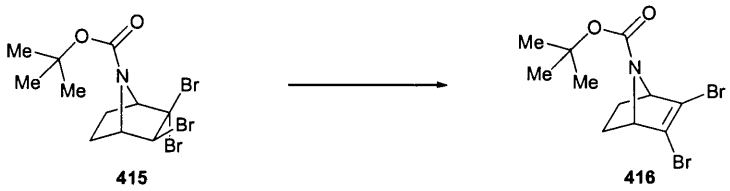


413 **414** **415**

Bromine (460 mg, 2.88 mmol) in hot CCl_4 (10 mL) was added dropwise to a solution of vinyl bromide **413** (750 mg, 2.74 mmol) in CCl_4 (15 mL) at 77°C. The solution of bromine was kept warm during the addition with a heat gun. The reaction was stirred for a further 10 min after the complete addition of the bromine. The reaction was then cooled to room temperature and $Na_2S_2O_3$ (10% solution, 20 mL) was added. The organic layer was separated and washed with $NaHCO_3$ (saturated solution, 2 x 10 mL) and water (2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol to 20:1, petrol:EtOAc) to give compounds in order of elution; *endo-tribromide* **414** (464mg, 39%) as a colourless crystalline solid; Mp 81-82°C; R_f (5:1, petrol:EtOAc) 0.63; ν_{max} (film) 1706 (C=O); δ_H (300 MHz) 4.99 (1H, dd, J = 4.6 and 1.3, C(H)Br-C_{brid}-***H***), 4.69 (1H, br s, CBr_2-C_{brid}-H), 4.33 (1H, br s, C(Br)-H_{exo}), 2.32-2.25 (1H, m, C(H)-***H***$_{endo}$), 2.05-1.97 (1H, m, C(H)-***H***$_{endo}$), 1.85-1.76 (1H, m, C(H)-***H***$_{exo}$), 1.75-1.65 (1H, m, C(H)-***H***$_{exo}$), 1.44 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz) 152.9 (quat., C=O), 81.2 (quat., $C(Me)_3$), 71.5 (CBr_2-***C***$_{brid}$-H), 67.1 (quat., CBr_2), 62.0 (C(H)Br-***C***$_{brid}$-H), 28.2 ($C(CH_3)_3$), 22.4 (CH_2), 21.7 (CH_2); *m/z* (FAB+) 437.9/435.9/433.9/431.9 (20%, (M+)), 381.8/379.8/377.8/375.8 (100%, (M+) - ^{t}Bu,), 356.0/354.0/352.0 ((M+) - Br), 299.9/297.9/295.9 ((M+) - Br, - ^{t}Bu), 255.9/253.9/251.9 ((M+) - Br, - $CO_2{}^t$Bu), 220.0/218.0 ((M+) - 2 x Br, - ^{t}Bu); Found (FAB+) 433.8784; $C_{11}H_{17}{}^{79}Br_2{}^{81}BrNO_2$ (M+H), requires 433.8789. And *exo-tribromide* **415** (494 mg, 42%) as a colourless crystalline solid; Mp 59-61°C; R_f (5:1, petrol:EtOAc) 0.44; ν_{max} (film) 1708 (C=O); δ_H (300 MHz) 4.73 (1H, br s, CBr_2-C_{brid}-H), 4.34-4.21 (2H, m, C(Br)-***H***$_{endo}$-C_{brid}-***H***), 2.40-2.34 (1H, m, C(H)-***H***$_{endo}$), 1.80 (2H, br s, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.60-1.54 (1H, m, C(H)-***H***$_{endo}$), 1.41 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz) 152.9 (quat., C=O), 80.8 (quat., $C(Me)_3$), 72.2 (CBr_2-***C***$_{brid}$-H), 71.5 (CBr_2-***C***$_{brid}$-H), 68.8 (quat., CBr_2), 66.5 (C-H), 65.8 (C-H), 65.0 (C-H), 64.6 (C-H), 28.9 (CH_2), 28.5 (CH_2), 28.1 ($C(CH_3)_3$), 26.5 (CH_2), 26.2 (CH_2); *m/z* (FAB+) 437.8/435.8/433.8/431.8 (20%, (M+)), 381.8/379.8/377.8/375.8 (100%, (M+) - ^{t}Bu), 355.9/353.9/351.9 ((M+) - Br), 299.9/297.9/277.9 ((M+) - Br, - ^{t}Bu), 255.9/253.9/251.9 ((M+) - Br, - $CO_2{}^t$Bu), 220.0/218.0 ((M+) - 2 x Br, - ^{t}Bu); Found (FAB+) 433.8783; $C_{11}H_{17}{}^{79}Br_2{}^{81}BrNO_2$ (M+H), requires 433.8789.

The reaction, when repeated on a 3.3 gram scale (of **413**) gave a mixture of tribromides **414** and **415** in a 96% yield.

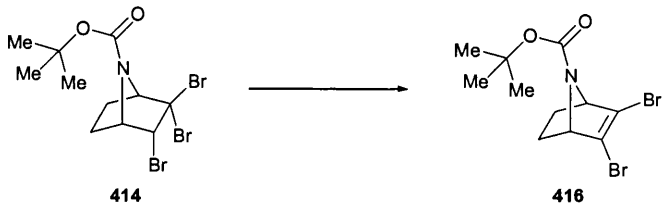
2,3-Dibromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 416



415 **416**

KO^{t}Bu (48 mg, 0.409 mmol) was added to a stirring solution of *exo*-tribromide **415** (170 mg, 0.392 mmol) in THF (8 mL) at 0°C. A white ppt. begins to form almost immediately after the addition of the base. The reaction was stirred for 5 mins before the ice bath was removed and the reaction was allowed to return to room temperature. The reaction was stirred for an additional 90 mins. The reaction mixture was then filtered through a pad of silica and washed through with DCM (3 x 15 mL). The solvent was then concentrated *in vacuo* to yield *vinyl dibromide* **416** (132 mg, 96%) as a colourless crystalline solid; Mp 61-62°C; R_f (5:1, petrol:EtOAc) 0.77; ν_{max} (film) 1715 (C=O), 1585 (C=C); δ_H (300 MHz) 4.61 (2H, br s, 2 x C_{brid}-H), 1.92-1.88 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.40 (9H, s, $C(CH_3)_3$), 1.38-1.34 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}); δ_C (75.5 MHz) 154.4 (quat., C=O), 124.8 (quat., 2 x C_{vin}-Br), 80.5 (quat., $C(Me)_3$), 67.2 (2 x C_{brid}-H), 27.9 ($C(CH_3)_3$), 25.0 (2 x CH_2); *m/z* (FAB+) 355.9/353.9/351.9 (30%, (M+H)), 326.9/324.9/322.9 ((M+) - CH_2=CH_2), 299.9/297.9/295.9 (100%, (M+H) - ^{t}Bu,) 255.9/253.9/251.9 ((M+H) - $CO_2{}^t$Bu); Found (FAB+) 353.9529; $C_{11}H_{16}{}^{79}Br^{81}BrNO_2$ (M+H), requires 353.9527; Analysis calculated for $C_{11}H_{15}Br_2NO_2$, C = 37.42%, H = 4.28%, N = 3.97%; Found C = 37.47%, H = 4.23%, N = 3.90%.

2,3-Dibromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 416



414 **416**

KO^{t}Bu (48 mg, 0.409 mmol) was added to a stirring solution of *endo*-tribromide **414** (170 mg, 0.392 mmol) in THF (8 mL) at 0°C. A white ppt. begins to form almost immediately after the addition of the base. The reaction was stirred for 5 minutes before the ice bath was removed and the reaction was allowed to return to room temperature. The reaction was stirred for an additional 90 mins. The reaction mixture was then filtered through a pad of silica and washed through with DCM (3 x 15 mL). The solvent was then concentrated *in vacuo* to yield vinyl *dibromide* **416** (132mg, 96%) as a colourless crystalline solid, data as before.

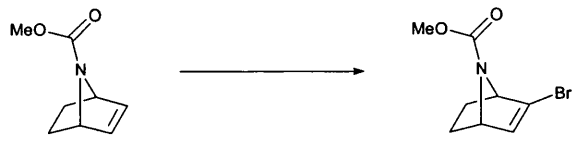
Methyl carbamate dibromide 402

7-Aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid methyl ester 165[2]

171 **165**

TFA (0.355 mL, 4.61 mmol) was added to a stirring solution of BOC-alkene **171** (450 mg, 2.30 mmol) in DCM (6 mL) at room temperature. The reaction was stirred for two hours and the reaction mixture was then concentrated *in vacuo*. The residue was dissolved in THF (15 mL), cooled to 0°C and stirred. Pyridine (0.745 mL, 9.22 mmol) was added dropwise, followed by methyl chloroformate (0.356 mL, 4.61 mmol) and the reaction mixture was allowed to return to room temperature and stirred overnight. The reaction mixture was then concentrated *in vacuo* and the residue was taken up in EtOAc (20 mL) and washed with water (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (10:1, petrol:EtOAc) to yield methyl carbamate **165** (247 mg, 70%) as a colourless oil, data as above

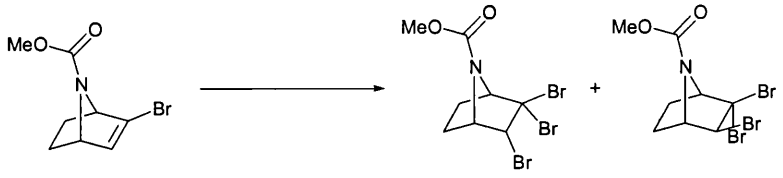
2-Bromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid methyl ester 399



165 **399**

Phenyl selenium bromide (305 mg, 1.293 mmol) was added to a solution of alkene **165** (180 mg, 1.175 mmol) in $CHCl_3$ (6 mL) at room temperature. The reaction was stirred for two hours. The solvent was then removed *in vacuo* and the residue was dissolved in THF (15 mL) and cooled to 0°C. $NaHCO_3$ (148 mg, 1.76 mmol) was added followed by H_2O_2 (35%w/w solution in H_2O, 855 mg, 8.8 mmol) and the reaction was allowed to return to room temperature and stirred overnight. EtOAc (30 mL) was added and the reaction mixture was washed with water (2 x 15mL). The organic layer was dried ($NaSO_4$), filtered and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol-10:1, petrol:EtOAc) to give the *vinyl bromide* **399** (218 mg, 79%) as a colourless oil; R_f (5:1, petrol:EtOAc) 0.54; ν_{max} (film), 1718 (C=O), 1575 (C=C); δ_H (300 MHz) 6.27 (1H, s, C_{vin}-H), 4.73 (1H, s, C_{brid}-H), 4.64 (1H, s, C_{brid}-H), 3.65 (3H, s, OCH_3), 1.95-1.87 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.34-1.27 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}); δ_C (75.5 MHz) 155.5 (quat., C=O), 134.1 (C_{vin}-H), 123.2 (quat., C_{vin}-Br), 65.4 (C_{brid}-H), 61.7 (C_{brid}-H), 52.5 (OCH_3), 25.4 (CH_2), 23.6 (CH_2); *m/z* (CI+) 251.1/249.1 (15%, $(M+NH_4)$), 234.1/232.1 (20%, (M+H)), 172.2 ($(M+NH_4)$ - Br), 155.2 (100%, (M+H) - Br); Found (ES+) 231.9968; $C_8H_{11}{}^{79}BrNO_2$ (M+H), requires 231.9973.

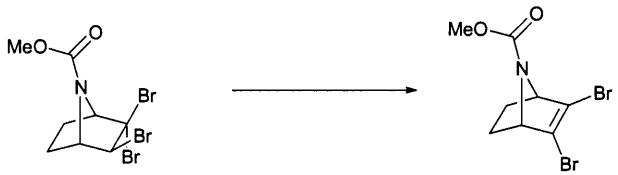
2,2,3-*endo*-Tribromo-7-aza-bicyclo[2.2.1]heptane-7-carboxylic acid methyl ester 403 and 2,2,3-*exo*-Tribromo-7-aza-bicyclo[2.2.1heptane-7-carboxylic acid methyl ester 404



399 **403** **404**

Bromine (166 mg, 1.04 mmol) in hot CCl_4 (10 mL) was added dropwise to a solution of vinyl bromide **399** (220 mg, 0.948 mmol) in CCl_4 (5 mL) at 77°C. The solution of bromine was kept warm during the addition with a heat gun. The reaction was stirred for a further 10 min after the complete addition of the bromine and then cooled to room temperature and $Na_2S_2O_3$ (10% solution, 10 mL) was added. The organic layer was separated and washed with $NaHCO_3$ (saturated solution, 2 x 10 mL) and water (2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol to 10:1, petrol:EtOAc) to give compounds in order of elution; *endo tribromide* **403** (207 mg, 56%) as a colourless oil; R_f (5:1, petrol:EtOAc) 0.50; ν_{max} (film) 1716 (C=O); δ_H (300 MHz) 5.03 (1H, dd, J = 4.6 and 1.5, C(Br)-H_{exo}), 4.78 (1H, br s, CBr_2-C_{brid}-H), 4.40 (1H, br s, C(H)Br-C_{brid}-***H***), 3.73 (3H, s, OCH_3), 2.37-2.29 (1H, m, CBr_2-C_{brid}-C(H)-H_{endo}), 2.13-2.04 (1H, m, C(H)Br-C_{brid}-C(H)-H_{endo}), 1.88-1.65 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}); δ_C (75.5 MHz) 153.6 (quat., C=O), 71.7 (CBr_2-C_{brid}-H), 66.5 (quat., CBr_2), 63.7 (C(Br)-H), 61.9 (C(H)Br-C_{brid}-H), 52.9 (OCH_3), 27.9 (C(H)Br-C_{brid}-CH_2), 22.1 (CBr_2-C_{brid}-CH_2); *m/z* (FAB+) 395.9/393.9/391.9/389.9 (100%, (M+H)), 314.0/312.0/308.0 (80%, (M+H) - Br), 234.1/232.1 ((M+H) - 2 x Br); Found (FAB+) 391.8316; $C_8H_{11}{}^{79}Br_2{}^{81}Br\ NO_2$ (M+H), requires 391.8319. And *exo-tribromide* **404** (68mg, 28%) as a colourless crystalline solid; Mp 102-103°C; R_f (5:1, petrol:EtOAc) 0.31; ν_{max} (film) 1713 (C=O); δ_H (300 MHz) 4.83 (1H, br s, CBr_2-C_{brid}-H), 4.40 (1H, br s, C(H)Br-C_{brid}-***H***), 4.37 (1H, s, C(Br)-H_{endo}), 3.71 (3H, s, OCH_3), 2.43 (1H, app. t, J = 9.1, C(H)-H_{endo}), 1.86-1.83 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.63 (1H, app. t, J = 8.6, C(H)-H_{endo}); δ_C (75.5 MHz) 153.5 (quat., C=O), 72.3 (CBr_2-C_{brid}-H), 68.3 (quat., CBr_2), 66.6 (C(H)Br-C_{brid}-***H***), 64.5 (C(H)-Br), 52.9 (CO_2CH_3), 28.8 (CH_2), 26.3 (CH_2); *m/z* (CI+) 395.6/393.6/391.6/389.6 (50%, (M+H)), 313.7/311.7/309.7 (100%, (M+H) - Br), 249.8/247.8 ((M+NH_4) - Br_2), 233.8/231.8 ((M+H) - 2 x Br), 204.8/202.8 ((M+) - 2 x Br, - CH_2=CH_2); Found (CI+) 389.8337; $C_8H_{11}{}^{79}Br_3NO_2$ (M+H), requires 389.8340. For X-ray crystal structure and data for *exo*-tribromide **404**, see Appendix B.

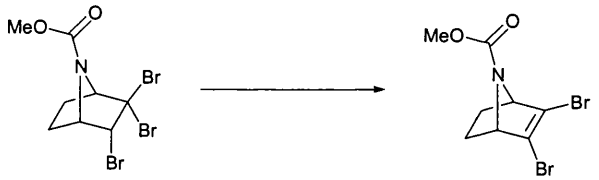
2,3-Dibromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid methyl ester 402



404 **402**

KO^{t}Bu (33 mg, 0.28 mmol) was added to a stirring solution of tribromide **404** (100 mg, 0.254 mmol) in THF (5 mL) at 0°C. The reaction was stirred for 20 mins before the ice bath was removed and the reaction was allowed to return to room temperature. The reaction was stirred for an additional 90 mins, in which time a white ppt. gradually forms. The reaction was filtered through a pad of silica and washed through with DCM (3 x 8 mL). The solvent was then concentrated *in vacuo* to yield *vinyl dibromide* **402** (72 mg 91%) as a colourless oil; R_f (5:1, petrol:EtOAc) 0.33; ν_{max} (film) 1728 (C=O), 1584 (C=C); δ_H (300 MHz) 4.71 (2H, br s, 2 x C_{brid}-H), 3.68 (3H, s, OCH_3), 1.96-1.92 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.44-1.40 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}); δ_C (75.5 MHz) 155.6 (quat., C=O), 126.6 (quat., 2 x C_{vin}-Br), 67.2 (2 x C_{brid}-H), 53.0 (OCH_3), 25.4 (2 x CH_2); *m/z* (CI+) 330.8/328.8/326.8 (100%, (M+NH_4)), 313.8/311.8/309.8 (60%, (M+H)), 284.8/282.8/280.8 ((M+) - CH_2=CH_2), 250.9/248.9 ((M+NH_4) - Br), 233.9/231.9 ((M+H) - Br), 204.8/202.8 ((M+) - CH_2=CH_2, - Br); Found (ES+) 326.9343; $C_8H_{13}{}^{79}Br_2N_2O_2$ (M+NH_4), requires 326.9344.

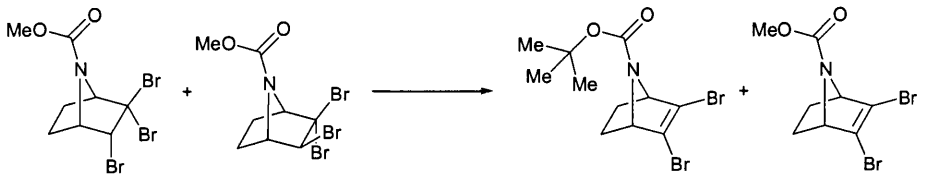
2,3-Dibromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid methyl ester 402



403 **402**

KO^{t}Bu (23 mg, 0.245 mmol) was added to a stirring solution of tribromide **403** (80 mg, 0.204 mmol) in THF (4 mL) at 0°C. The reaction was stirred for 20 mins before the ice bath was removed and the reaction was allowed to return to room temperature. The reaction was stirred for an additional 90 mins, in which time a white ppt. gradually forms. The reaction was filtered through a pad of silica and washed through with DCM (3 x 6 mL). The solvent was then concentrated *in vacuo* to yield *vinyl dibromide* **402** (57 mg, 90%) as a colourless oil, data as before.

2,3-Dibromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid methyl ester 402 and 2,3-Dibromo-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 416



403 **404** **416** **402**

KO^{t}Bu (64 mg, 0.572 mmol) was added to a stirring solution of tribromides **403** and **404** (112 mg, 0.286 mmol) in THF (6 mL) at 0°C. The reaction was stirred for 20 mins before the ice bath was removed and the reaction was allowed to return to room temperature. The reaction was stirred for an additional 5 hours, in which time a white ppt. had formed. The reaction was filtered through a pad of silica and washed through with DCM (3 x 10mL). The solvent was then concentrated *in vacuo* to yield a colourless oil that was purified *via* flash chromatography (10:1, petrol:EtOAc) to yield in order of elution BOC *dibromide* **416** (48 mg, 48%) as a colourless solid, data as above. And methyl carbamate dibromide **402** (36 mg, 41%) as a colourless oil, data as above.

Free amine **417**

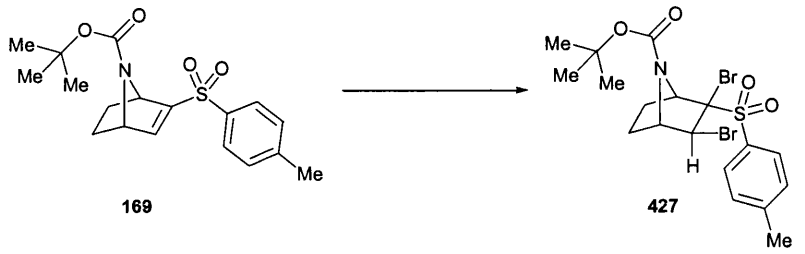
2,3-Dibromo-7-aza-bicyclo[2.2.1]hept-2-ene 417

416 **417**

TFA (0.262 mL, 3.40 mmol) was added slowly to a solution of dibromide **416** (600 mg, 1.70 mmol) and anisole (0.92 mL, 8.5 mmol) in DCM (5 mL) at 0°C. The reaction mixture was allowed to return to room temperature and stir overnight. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (25 mL) and washed with Na_2CO_3 (2 M solution, 3 x 15 mL) before drying (Na_2SO_4). The solvent was then removed *in vacuo* to yield *amine* **417** (401 mg, 93%) as a light beige solid. Sublimation (50°C, ~50 mmHg) provided colourless crystalline material; Mp 70-71°C; ν_{max} (film) 3159 (N-H), 1587 (C=C); δ_H (300 MHz) 4.09 (2H, br s, 2 x C_{brid}-H), 2.17 (1H, ex. br s, N-H), 1.85 (2H, app. br d, J = 8.0, H_{exo}-C(H)-C(H)-H_{exo}), 1.31 (2H, app. br d, J = 7.4, H_{endo}-C(H)-C(H)-H_{endo}); δ_C (75.5 MHz) 128.5 (quat., 2 x C_{vin}-Br), 67.6 (2 x C_{brid}-H), 24.7 (2 x CH_2); *m/z* (CI+) 272.8/270.8/268.8 ($M+NH_4$), 255.8/253.8/251.8 (100%, (M+H)), 226.8/224.8/222.8 ((M+) - CH_2=CH_2), 175.8/173.8 ((M+H) - Br), 96.0 ((M+H) - 2 x Br); Found (ES+) 251.9026; $C_6H_8Br_2N$ (M+H), requires 251.9023.

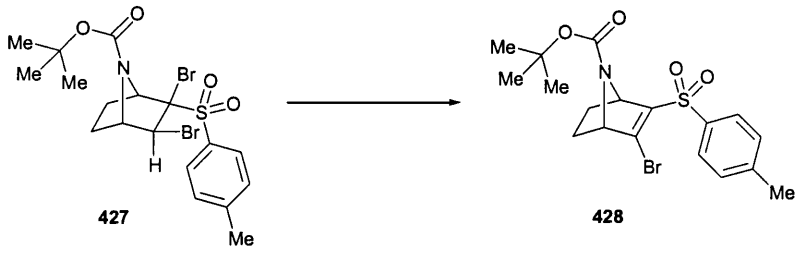
Attempted synthesis of dibromide **416** *via selective elimination*

2-(Toluene-4-sulphonyl)-2-bromo-3-bromo-7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptane 427



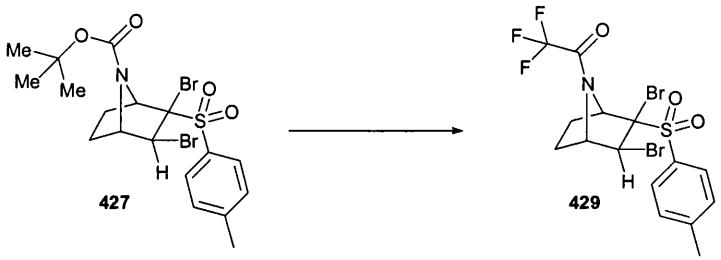
Bromine (274 mg, 1.72 mmol) in hot CCl_4 (20 mL) was added dropwise to a solution of vinyl sulphone **169** (500 mg, 1.43 mmol) in CCl_4 (50 mL) at 77°C. The bromine solution was kept warm throughout the addition by the use of a heat gun. The reaction mixture was then heated to reflux (oil bath temperature increased to 95°C) and stirred for 6 hours. The reaction mixture was then cooled and $Na_2S_2O_3$ (10% solution, 20 mL) was added. The organic layer was then separated, washed with Na_2CO_3 (10% solution, 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified *via* flash chromatography, (gradient elution, petrol to 4:1, petrol:EtOAc) to yield in order of elution, vinyl sulphone **169** (35 mgs, 7% recovery). And *dibromide* **427** (180 mg, 85%), as a colourless solid; Mp discolours gradually from 151°C, melts and decomposes 157-158°C; R_f (2:1 petrol:EtOAc) 0.65; ν_{max} (film) 1707 (C=O); δ_H (300 MHz) 7.80 (2H, d, J = 8.2, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.36 (2H, d, J = 8.2, Me-C_{ar}-(C_{ar}-H)$_2$), 4.86 (1H, br s), 4.82 (1H, br s), 4.55-4.50 (1H, m), 2.77-2.70 (1H, m), 2.46 (3H, s, C_{ar}-CH_3), 1.90-1.80 (3H, m), 1.45 (9H, s, C(CH_3)$_3$); δ_C (75.5 MHz) 153.1 (quat., C=O), 146.0 (quat., Me-C_{ar}), 134.0 (quat., SO_2-C_{ar}), 130.4 (Me-C_{ar}-(C_{ar}-H)$_2$), 129.5 (SO_2-C_{ar}-(C_{ar}-H)$_2$), 88.4 (quat., C(Br)-SO_2), 81.4 (quat., C(Me)$_3$), 69.3 (C_{brid}-H), 68.6 (C_{brid}-H), 67.8 (C_{brid}-H), 67.1 (C_{brid}-H), 54.4 (C(H)-Br), 29.0 (CH_2), 28.4 (CH_2), 28.2 (C(CH_3)$_3$), 26.0 (CH_2), 25.3 (CH_2); *m/z* (CI+) 528.9/526.9/524.9 ($M+NH_4$), 511.9/509.9/507.9 (25%, (M+H)), 473.0/471.0/469.0 ((M+H) - ^{t}Bu)), 412.0/410.0/408.0 ((M+H) - $CO_2{}^t$Bu)), 367.2 (($M+NH_4$) - 2 x Br), 350.2 ((M+H) - 2 x Br), 250.1 (100%, (M+H) - 2 x Br, - $CO_2{}^t$Bu); Found (ES+) 507.9788; $C_{18}H_{24}{}^{79}Br_2NO_4S$ (M+H) requires 507.9793; Analysis calculated for $C_{18}H_{23}Br_2NO_4S$, C = 42.4%, H = 4.55%, N = 2.75%; Found C = 42.0%, H = 4.39%, N = 2.67%.

2-Bromo-3-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 428



KO^{t}Bu (49 mg, 0.432 mmol) was added to a stirring solution of dibromide **427** (200 mg, 0.393 mmol) in THF (5 mL) at 0°C. The reaction mixture begins to cloud with a white ppt. on addition of the base. The reaction was allowed to return to room temperature and stirred for two hours. EtOAc (30 mL) was then added and the reaction mixture was washed with water (3 x 10 mL) and then brine (1 x 10 mL). The organic layer was dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was purified *via* flash chromatography (10:1, petrol:EtOAc) to yield *vinyl bromide* **428** (138mg, 82%) as a colourless crystalline solid; R_f (5:1, petrol:EtOAc) 0.36; ν_{max} (film) 1714 (C=O), 1328 (SO_2), 1155 (SO_2); δ_H (300 MHz) 7.84 (2H, d, J = 8.3, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.34 (2H, d, J = 8.3, Me-C_{ar}-(C_{ar}-H)$_2$), 4.89-4.88 (1H, m, C_{brid}-H), 4.66 (1H, br s, C_{brid}-H), 2.42 (3H, s, C_{ar}-CH_3), 2.02-1.97 (2H, m, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.49-1.37 (2H, m, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$), 1.24 (9H, s, C(CH_3)$_3$); δ_C (75.5 MHz) 154.5 (quat., C=O), 145.1 (quat., C_{ar}-Me), 137.2 (quat., C_{ar}-SO_2), 130.3 (quat., C_{vin}), 129.9 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 129.4 (quat., C_{vin}), 127.7 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 81.2 (quat., C(Me)$_3$), 69.8 (C_{brid}-H), 64.0 (C_{brid}-H), 27.7 (C(***C***H$_3$), 24.1 (2 x CH_2), 21.6 (C_{ar}-***C***H$_3$); *m/z* (FAB+) 430.1/428.1, (5%, (M+H)), 374.1/372.1 (100%, ((M+H) - ^{t}Bu), 356.1/354.1 ((M+H) - ^{t}Bu, - CH_2=CH_2), 330.1/328.1 ((M+H) - $CO_2{}^t$Bu), 301.1/299.1 ((M+) - $CO_2{}^t$Bu, - CH_2=CH_2); Found (FAB+) 428.0491, $C_{18}H_{23}{}^{79}BrNO_4S$ (M+H), requires 428.0531.

1-[2,3-Dibromo-2-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-7-yl]-2,2,2-trifluoro-ethanone 429

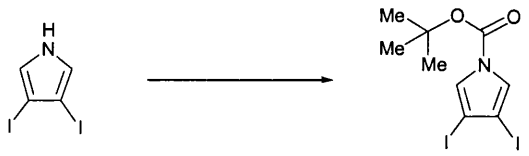


TFA (0.163mL, 2.12mmol) was added to a stirring solution of dibromide **427** (360 mg, 0.707 mmol) and anisole (0.614 mL, 5.65 mmol) in DCM (10 mL). The reaction was stirred at room temperature for 1 hour before being concentrated *in vacuo*. The residue was taken up in THF (20 mL) and cooled to 0°C. Pyridine (0.456 mL, 5.65 mmol) was added carefully dropwise followed by the addition of TsCl (270 mg, 1.41 mmol) the reaction was kept at 0°C for 20 mins before being allowed to return to room temperature and stirred overnight. EtOAc (50 mL) was then added and the reaction was washed with water (3 x 20 mL) and brine

(1 x 20 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (5:1, petrol/EtOAc) to yield *trifluoroacetamide* **429** (257 mg, 72%) as a colourless crystalline solid; Mp 145-146°C; R_f (3:1, petrol:EtOAc) 0.65; ν_{max} (film) 1703 (C=O), 1326 (SO_2), 1151 (SO_2); δ_H (300 MHz) 7.84-7.79 (2H, m, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.40 (2H, d, J = 8.3, Me-C_{ar}-(C_{ar}-H)$_2$), 5.26 (0.67H, dd, J = 4.1 and 1.6, C_{brid}-Ha), 5.09 (0.33H, br s, C_{brid}-Ha), 5.00 (1H, s, C(Br)-H_{endo}), 4.94 (0.67H, s, C_{brid}-Hb), 4.75 (0.33H, br s, C_{brid}-Hb), 2.96-2.85 (1H, m, C(H)-***H***$_{endo}$), 2.49 (3H, s, C_{ar}-CH_3), 2.10-1.85 (3H, m, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$ + C(H)-***H***$_{endo}$); δ_C (75.5 MHz) 146.7 (quat., Me-C_{ar}), 133.2 (quat., SO_2-C_{ar}), 130.5 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 129.7 (Me-C_{ar}-(C_{ar}-H)$_2$), 87.7 (quat., C(Br)-SO_2), 86.5 (quat., C(Br)-SO_2), 69.8 (C_{brid}-Hb), 68.6 (C_{brid}-Hb), 68.0 (C_{brid}-Ha), 67.1 (C_{brid}-Ha), 53.3 (C(Br)-H_{endo}), 52.3 (C(Br)-H_{endo}), 29.7 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 24.5 (CH_2), 21.8 (C_{ar}-***C***H_3); *m/z* (FAB+) 507.7/505.7/503.7 (85%, (M+H)), 425.8/423.8 ((M+H) - Br), 411.8/409.8/407.8 ((M+) - $COCF_3$), 345.9 (100%, (M+H) - 2 x Br), 316.9 ((M+) - 2 x Br, - CH_2=CH_2); Found (FAB+) 503.9096; $C_{15}H_{15}{}^{79}Br_2F_3NO_3S$ (M+H), requires 503.9091. For X-ray crystal structure and data for dibromide **429** compound see Appendix G.

Preparation of azabicyclo[2.2.1]heptadiene diiodide **423**

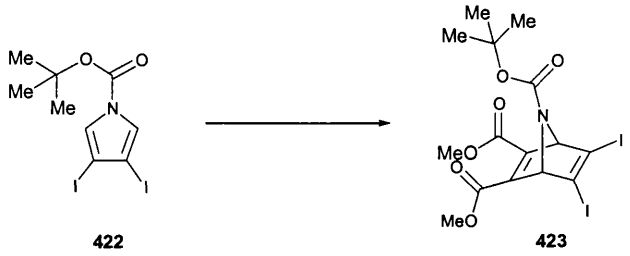
3,4-Diiodo-pyrrole-1-carboxylic acid *tert*-butyl ester 422



421 **422**

DMAP (14 mg, 0.113 mmol) and BOC_2O (135 mg, 0.621 mmol) were added to a solution of the diiodo pyrrole **421** (180 mg, 0.565 mmol) in DCM (10 mL). The reaction was stirred overnight. The reaction mixture was then concentrated *in vacuo* and the residue taken up in of EtOAc (20 mL). The organic layer was washed with water (2 x 10 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol to 10:1, petrol:EtOAc) to yield protected *pyrrole* **422** (227mg, 96%) as a colourless solid; Mp 83-84°C; R_f (5:1, petrol:EtOAc) 0.74; ν_{max} (film) 1748 (C=O); δ_H (400 MHz) 7.31 (2H, s, 2 x C_{vin}-H), 1.58 (9H, s, C(CH_3)$_3$); δ_C (100 MHz) 146.5 (quat., C=O), 125.7 (2 x C_{vin}-H), 85.5 (quat., 2 x C_{vin}-I), 78.5 (quat., C(Me)$_3$), 28.3 (C(***C***H_3)$_3$); *m/z* (CI+) 420 (100%, (M+H)); (EI+) 418.9 (50%, (M+)), 362.9 ((M+) - ^{t}Bu), 318.9 ((M+) - $CO_2{}^t$Bu), 290.1 ((M+) - I), 192 ((M+) - $CO_2{}^t$Bu, - I), 126.9 (I+), 57.2 (100%, (+^{t}Bu)); Found (ES+) 418.8878; $C_9H_{11}I_2NO_2$ (M+), requires 418.8879; Analysis calculated for $C_9H_{11}I_2NO_2$, C = 25.8%, H = 2.65%, N = 3.34%; Found C = 26.2%, H = 2.74%; N = 3.3%.

5,6-Diiodo-7-aza-bicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylic acid 7-*tert*-butyl ester dimethyl ester 423



Method 1

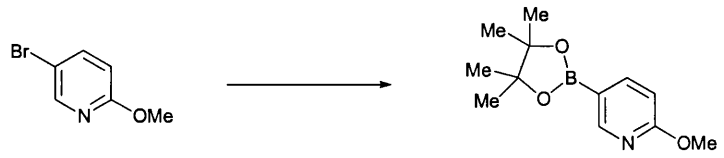
Protected pyrrole **422** (100 mg, 0.239 mmol) was dissolved in DMAD (339 mg, 2.39 mmol) and heated to 120°C for 4 hours. The reaction mixture was then allowed to cool to room temperature and the resulting dark oil was distilled under vacuum to remove the excess DMAD. The remaining residue was purified by flash chromatography (gradient elution, petrol to 10:1, petrol: EtOAc) to give bicyclic *diester* **423** (107 mg, 80%) as a yellow solid.

Method 2

Protected pyrrole **422** (100 mg, 0.239 mmol) and DMAD (62 mg, 0.478mmol) were dissolved in toluene (4 mL) and heated to reflux for 12 hours. The reaction mixture was then allowed to cool to room temperature reaction mixture was concentrated *in vacuo*. The resulting dark oil was purified by flash chromatography (gradient elution, petrol-10:1, petrol:EtOAc) to give bicyclic *diester* **423** (110 mg, 82%) as a yellow solid; Mp 131-132°C; R_f (5:1, petrol:EtOAc) 0.31; ν_{max} (film) 1720 (C=O); δ_H (400 MHz) 5.42 (2H, br s, 2 x C_{brid}-H), 3.84 (6H, s, 2 x OCH_3), 1.41 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 162.0 (quat., 2 x MeO(C=O), 153.3 (quat., ^{t}BuO(C=O), 149.3 (quat., 2 x C_{vin}-CO_2Me), 84.0 (quat., 2 x C_{vin}-I), 78.5 (quat., $C(Me)_3$), 52.6 (2 x C_{brid}-H), 27.8 ($C(CH_3)_3$); *m/z* (CI+) 579.1 (15%, $(M+NH_4)$), 562.0 (M+H), 523 ($(M+NH_4)$ - ^{t}Bu), 479.0 ($(M+NH_4)$ - $CO_2{}^t$Bu), 462.0 ((M+H) - $CO_2{}^t$Bu), 447.0 ((M+H) - $CO_2{}^t$Bu, - CH_3), 353.1 ($(M+NH_4)$ - $CO_2{}^t$Bu, - I), 336.1 ((M+H) - $CO_2{}^t$Bu, - I); Found (ES+) 561.9231; $C_{15}H_{18}I_2NO_6$, (M+H), requires 561.9224; Analysis calculated for $C_{15}H_{17}I_2NO_6$, C = 32.1%, H = 3.05%, N = 2.5%; Found C = 32.2%, H = 3.07%, N = 2.37%.

Preparation of pyridyl boronic esters

2-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine 434



67 **434**

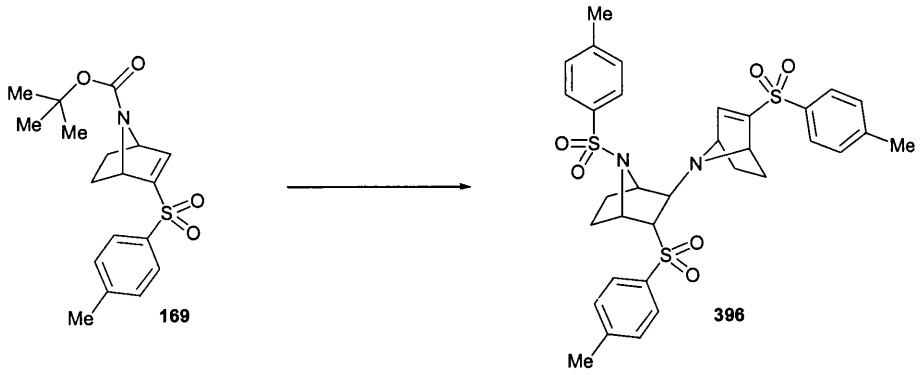
DMSO (15 mL) was added to a flask containing, pyridine **67** (500 mg, 2.66 mmol), *bis*(pinacolato)diboron **433** (1.351 g, 5.32 mmol), KOAc, (783 mg, 7.98 mmol) and $PdCl_2$(dppf).DCM (65 mg, 0.0798 mmol). The reaction mixture was heated to 80°C and stirred for 6 hours. The reaction was then allowed to cool and benzene (30 mL) was added. The reaction mixture was washed with water (3 x 10 mL) and the organic layer was separated and dried (Na_2CO_3). Concentration *in vacuo* resulted in a crude residue that was purified *via* Kugelrohr distillation to yield a 7:3 mixture of boronic ester **434** (~400 mg, 64%) and unreacted diboron **433** (~185 mg, 14%) as a colourless solid; ν_{max} (film) 1356 (B-O); δ_H (300 MHz) 8.53 (1H, s, N-C_{ar}-H), 7.92-7.88 (1H, m, B-C_{ar}-C_{ar}-H), 6.71-6.68 (1H, m, C_{ar}(Cl)-C_{ar}-H), 3.94 (3H, m, OCH_3), 1.34-1.31 (12H, m, 4 x CH_3); δ_C (75.5 MHz) 166.1 (quat., C_{ar}-OMe), 154.3 (N-C_{ar}-H), 145.4 (C_{ar}(OMe)-C_{ar}(H)-C_{ar}-H), 116.3 (quat., C_{ar}-BO_2), 109.4 (C_{ar}(Cl)-C_{ar}-H), 83.8 (quat., 2 x C(Me)$_2$), 53.4 (C_{ar}-OCH_3), 24.8 (2 x C-(CH_3)$_2$); *m/z* (FAB+) 236.3 (100%, (M+H)); Found (FAB+) 236.1450; $C_{12}H_{19}{}^{11}BNO_3$ (M+H), requires 236.1458.

2-Chloro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine 435

145 **435**

DMSO (12 mL) was added to a flask containing, pyridine **145**, (500 mg, 2.089 mmol), *bis*(pinacolato)diboron **433** (1.061 g, 4.18 mmol), KOAc, (615 mg, 6.27 mmol) and $PdCl_2$(dppf).DCM (51 mg, 0.0627 mmol). The reaction mixture was heated to 80°C and stirred for 2 hours. The reaction was then allowed to cool to room temperature and benzene (30 mL) was added. The reaction mixture was washed with water (3 x 10 mL) and the organic layer was separated and dried (Na_2CO_3). Concentration *in vacuo* left a crude residue that was purified *via* Kugelrohr distillation to yield a 7:3 mixture boronic ester **435** (~335mg, 67%) and unreacted diboron **433** (~152 mg, 14%) as a colourless solid; ν_{max} (film) 1356 (B-O); δ_H (300 MHz) 8.63 (1H, s, N-C_{ar}-H), 7.92 (1H, d, J = 7.9, C_{ar}(Cl)-C_{ar}-H), 7.23 (1H, d, J = 7.9, C_{ar}(Cl)-C_{ar}(H)-C_{ar}-*H*), 1.26 (12H, s, 4 x CH_3); δ_C (75.5 MHz) 155.6 (C_{ar}-H), 154.1 (quat., C_{ar}), 144.7 (C_{ar}-H), 124.6 (quat., C_{ar}), 123.7 (C_{ar}-H), 84.4 (quat., 2 x C(Me)$_2$), 24.7 (4 x CH_3); *m/z* (FAB+) 240.2/242.2 (90%, (M+H)); Found (FAB+) 240.0963; $C_{11}H_{16}{}^{11}B^{35}ClNO_2$ (M+H), requires 240.0963.

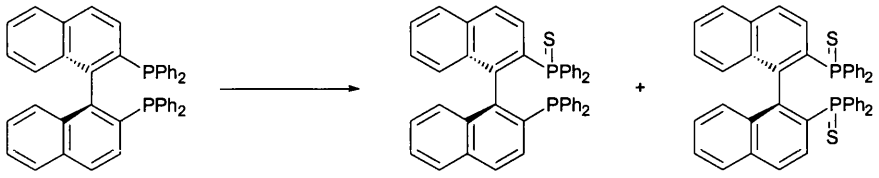
3,7,2'-Tris-(toluene-4-sulphonyl)-[2,7']bi[7-aza-bicyclo[2.2.1]heptyl]-2'-ene 396



TFA (2.51 mL, 32.6 mmol) was added to BOC vinyl sulphone **169** (5.7 g, 16.3 mmol) and the reaction mixture was stirred overnight. The excess TFA was then removed *in vacuo* and the residue diluted with EtOAc (100 mL) and washed with Na_2CO_3 (10% solution, 4 x 20 mL). The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in THF (100 mL) and TsCl (6.22 g, 32.6 mmol) and NEt_3 (6.82 mL, 48.9 mmol) were added and the reaction mixture was stirred overnight. The reaction mixture was then diluted with EtOAc (100 mL), washed with water (3 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, 10:1 to 3:1, petrol:EtOAc) to give *dimer* **396** (7.33 g, 69%) as a colourless crystalline solid; Mp 159-160°C; R_f (2:1, petrol:EtOAc) 0.33; ν_{max} (film) 1594 (C=C), 1314 (SO_2), 1151 (SO_2); δ_H (400 MHz) 7.83-7.81 (2H, m, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.72-7.67 (4H, m, 2 x SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.40-7.37 (4H, m, 2 x Me-C_{ar}-(C_{ar}-H)$_2$), 7.25-7.21 (2H, m, Me-C_{ar}-(C_{ar}-H)$_2$), 6.72 (1H, d, J = 2.0, C_{vin}-H), 3.94 (1H, app. d, J = 2.2, C_{vin}(H)-C_{brid}-***H***), 3.91-3.89 (1H, app t, J = 5.1, SO_2-C(H_{exo})-C_{brid}-***H***), 3.83 (1H, d, J = 3.6, SO_2-C_{vin}-C_{brid}-***H***), 3.50 (1H, d, J = 4.4, R_2N-C(H_{endo})-C_{brid}-***H***), 3.28 (1H, app. t, J = 3.6, SO_2-C-***H***$_{exo}$), 2.48 (1H, d, J = 3.6, R_2N-C-***H***$_{endo}$), 2.46 (3H, s, C_{ar}-CH_3), 2.44 (3H, s, C_{ar}-CH_3), 2.40 (3H, s, C_{ar}-CH_3), 2.33-2.26 (1H, m, heptane ring, C(H)-***H***$_{endo}$), 1.85-1.76 (2H, m, heptene ring, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.59-1.50 (2H, m, heptane ring, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.19-1.06 (2H, m, heptene, ring ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$), 0.93-0.87 (1H, m, heptane ring, C(H)-***H***$_{endo}$); δ_C (100 MHz) 145.9 (quat., SO_2-C_{vin}), 145.4 (quat., Me-C_{ar}), 144.5 (quat., Me-C_{ar}), 143.5 (quat., Me-C_{ar}), 141.8 (C_{vin}-H), 137.6 (quat, SO_2-C_{ar}), 136.6 (quat., SO_2-C_{ar}), 135.7 (quat., SO_2-C_{ar}), 130.2 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 130.0 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 129.2 (Me-C_{ar}-(***C***$_{ar}$-H)$_2$), 127.9 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 127.7 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 127.0 (SO_2-C_{ar}-(***C***$_{ar}$-H)$_2$), 71.3 (SO_2-C-H_{exo}), 64.6 (R_2N-C(H)-***C***$_{brid}$-H), 64.3 (SO_2-C_{vin}-***C***$_{brid}$-H), 64.2 (C_{vin}(H)-***C***$_{brid}$-H), 60.7 (R_2N-C-H_{endo}), 60.4 (SO_2-C(H)-***C***$_{brid}$-H), 25.5 (heptane, CH_2), 25.4 (heptane, CH_2), 24.9 (heptene, CH_2), 24.2 (heptene, CH_2), 21.8 (C_{ar}-***C***H_3), 21.7 (C_{ar}-***C***H_3), 21.6 (C_{ar}-***C***H_3); *m/z* (FAB+) 653.1 (100%, (M+H)), 497.2 ((M+) - tosyl); Found (FAB+) 653.1815; $C_{33}H_{37}N_2O_6S_3$ (M+H), requires 653.1813; Analysis calculated for $C_{33}H_{36}N_2O_6S_3$, C = 60.7%, H = 5.56%, N = 4.29%; Found: C = 60.4%, H = 5.54%, N = 4.35%.

Synthesis of sulphonated ligands from C_2 symmetric diphosphines

(*R*)-[2'-(Diphenyl-phosphinothioyl)-[1,1']binaphthalenyl-2-yl]-diphenyl-phosphane 442 and (*R*)-2,2'-*Bis*-(diphenyl-phosphinothioyl)-[1,1']binaphthalenyl 443

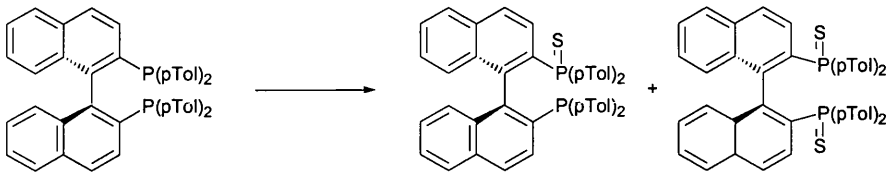


440 **442** **443**

Sulphur (12.4 mg, 0.385 mmol) was added to a stirring solution of (*R*)-BINAP (200 mg, 0.321 mmol) in degassed benzene (6 mL). The resulting solution was heated to reflux for 2.5 hours before being allowed to cool to room temperature. The solvent was removed *in vacuo* and the resulting residue was purified *via* flash chromatography (gradient elution, 10:1 to 5:1, petrol:EtOAc) to yield in order of elution; (*R*)-BINAP (40mgs, 20%). And *mono sulphide* **442** (78mg, 37%) as a colourless solid; Mp discolours above 225°C, decomposition begins at 243-244°C, melts at 250-251°C; R_f (5:1, petrol:EtOAc) 0.45; ν_{max} (film) 3052 (C_{ar}-H), 1584 (C=C), 1551 (C=C), 1502 (C=C), 1479 (C=C); δ_H (300 MHz) 7.86-7.72 (2H, m, 2 x C_{ar}-H) 7.66-7.41 (6H, m, 6 x C_{ar}-H), 7.35-7.30 (2H, m, 2 x C_{ar}-H), 7.24-7.12 (6H, m, 6 x C_{ar}-H), 7.09-6.96 (6H, m, 6 x C_{ar}-H), 6.86 (4H, app. t, J = 7.6, 4 x C_{ar}-H), 6.74 (2H, app. t, J = 7.9, 2 x C_{ar}-H), 6.38 (2H, app. t, J = 7.9, 2 x C_{ar}-H), 6.23 (2H, d, J = 8.5, 2 x C_{ar}-H); δ_C (75.5 MHz) 142.67 (quat., C_{ar}), 142.46 (quat., C_{ar}), 138.41 (quat., C_{ar}), 138.22 (quat., C_{ar}), 136.29 (quat., C_{ar}), 136.07 (quat., C_{ar}), 134.91 (C_{ar}-H), 134.61 (C_{ar}-H), 133.48 (C_{ar}-H), 138.25 (C_{ar}-H), 132.96 (quat., C_{ar}), 132.27 (C_{ar}-H), 132.13 (C_{ar}-H), 132.03 (C_{ar}-H), 131.91 (C_{ar}-H), 130.54 (C_{ar}-H), 130.51 (C_{ar}-H), 130.19 (C_{ar}-H), 130.15 (C_{ar}-H), 129.53 (C_{ar}-H), 128.62 (C_{ar}-H), 128.36 (C_{ar}-H), 128.08 (C_{ar}-H), 128.01 (C_{ar}-H), 127.94 (C_{ar}-H), 127.88 (C_{ar}-H), 127.78 (C_{ar}-H), 127.72 (C_{ar}-H), 127.67 (C_{ar}-H), 127.65 (C_{ar}-H), 127.49 (C_{ar}-H), 127.37 (C_{ar}-H), 127.29 (C_{ar}-H), 127.13 (C_{ar}-H), 127.04 (C_{ar}-H), 127.01 (C_{ar}-H), 126.19 (C_{ar}-H), 125.97 (C_{ar}-H), 125.70 (C_{ar}-H); δ_P (121.5 MHz) 45.24 (P=S), -14.44 (P); *m/z* (FAB+) 655.2 (20%, (M+H)), 469.2 ((M+) - PPh_2), 437.2 (100%, (M+) - S=PPh_2), 217.1 (S=PPh_2+); Found (FAB+) 655.1800; $C_{44}H_{33}P_2S$ (M+H), requires 655.1778; $[\alpha]_D^{20}$ = +35 ($CHCl_3$, c = 0.5). And *bis sulphide* **443** (60 mg, 27%) as a colourless solid; melting point: >315°C, discolours slightly over 303°C; R_f (5:1, petrol:EtOAc) 0.25; ν_{max} (film) 3053 (C_{ar}-H), 1586 (C=C), 1548 (C=C), 1501 (C=C), 1479 (C=C); δ_H (300 MHz) 7.82-7.65 (12H, m, (12 x C_{ar}-H)), 7.53-7.45 (4H, m, (4 x C_{ar}-H)), 7.32-7.24 (12H, m, (12 x C_{ar}-H)), 6.74 (2H, app. d, J = 8.4, (2 x C_{ar}-H)), 6.66 (2H, app. t, J = 7.1, (3 x C_{ar}-H)); δ_C (75.5 MHz) 140.50 (quat., C_{ar}), 140.43 (quat., C_{ar}), 140.32 (quat., C_{ar}), 136.14 (quat., C_{ar}), 134.99 (quat., C_{ar}), 133.91 (quat., C_{ar}), 133.88 (quat., C_{ar}), 133.39 (quat., C_{ar}), 133.23 (quat., C_{ar}), 132.80 (C_{ar}-H), 132.67 (C_{ar}-H), 132.14 (C_{ar}-H), 132.12 (quat., C_{ar}), 132.00 (C_{ar}-H) 131.01 (quat., C_{ar}), 130.83 (C_{ar}-H), 130.79 (C_{ar}-H), 130.55 (C_{ar}-H), 130.51 (C_{ar}-H), 129.34 (C_{ar}-H), 129.19 (C_{ar}-H), 129.03 (quat., C_{ar}), 128.02 (C_{ar}-H), 127.92 (quat., C_{ar}), 127.69 (C_{ar}-H), 127.69 (C_{ar}-H), 127.56 (C_{ar}-H), 127.39 (C_{ar}-H), 127.19 (C_{ar}-H), 125.60 (C_{ar}-H); δ_P (121.5 MHz) 43.70 (2 x (S=P)); *m/z* (FAB+) 687.1 (50%, (M+H)), 655.2 ((M+H) - S), 469.2 (100%, (M+) -

$S{=}PPh_2$), 437.2 ((M+) - $S{=}PPh_2$, - S), 217.1 ($S{=}PPh_2$+); Found (FAB+) 687.1479; $C_{44}H_{33}P_2S_2$ (M+H), requires 687.1499; $[\alpha]_D^{20}$ = +72 ($CHCl_3$, c = 0.5).

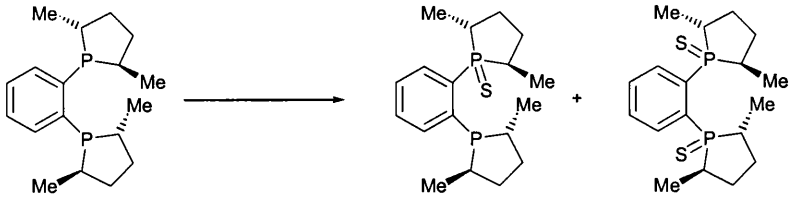
(*R*)-[2'-(Di-p-tolyl-phosphinothioyl)-[1,1']binaphthalenyl-2-yl]-di-p-tolyl-phosphane 445 and (*R*)-2,2'-*Bis*-(di-p-tolyl-phosphinothioyl)-[1,1']binaphthalenyl 446



444 **445** **446**

Sulphur (4.7 mg, 0.162 mmol) was added to a solution of (*R*)-TolBINAP (100 mg, 0.147 mmol) in degassed benzene (3 mL). The reaction mixture was heated to reflux for 2.5 hours before being cooled and the solvent removed *in vacuo*. The solid residue was purified *via* flash chromatography (gradient elution, petrol to 7:1, petrol:EtOAc) to yield in order of elution, (*R*)-TolBINAP as a colourless solid (20mg, 20%). And *mono-sulphide* **445**, (42mg, 40%) as a colourless solid, Mp >300°C; R_f (10:1, petrol:EtOAc) 0.29; ν_{max} (film) 3049 (C_{ar}-H), 1598 (C=C), 1551 (C=C), 1496 (C=C), 1448 (C=C); δ_H (300 MHz) 7.89-7.69 (2H, m, 2 x C_{ar}-H), 7.62 (1H, d, J = 8.1, C_{ar}-H), 7.48-7.30 (5H, m, 5 x C_{ar}-H), 7.24-7.18 (3H, m, 3 x C_{ar}-H), 7.10 (1H, t, J = 6.9, C_{ar}-H), 7.02-7.00 (3H, m, 3 x C_{ar}-H), 6.89-6.75 (6H, m, 6 x C_{ar}-H), 6.65-6.57 (5H, m, 5 x C_{ar}-H), 6.36 (1H, t, J = 7.5, C_{ar}-H), 6.18 (1H, d, J = 8.5, C_{ar}-H), 2.23 (3H, s, C_{ar}-CH_3), 2.13 (3H, s, C_{ar}-CH_3), 2.10 (3H, s, C_{ar}-CH_3), 2.07 (3H, s, C_{ar}-CH_3); δ_C (75.5 MHz) 141.85 (C_{ar}), 140.3 (C_{ar}), 134.8 (C_{ar}), 134.5 (C_{ar}), 133.5 (C_{ar}), 133.2 (C_{ar}), 132.1 (C_{ar}), 128.8 (C_{ar}), 128.1 (C_{ar}), 128.02 (C_{ar}), 127.95 (C_{ar}), 127.90 (C_{ar}), 127.84 (C_{ar}), 127.80 (C_{ar}), 127.04 (C_{ar}), 126.98 (C_{ar}), 126.04 (C_{ar}), 125.89 (C_{ar}), 21.2 (C_{ar}-CH_3), 21.1 (C_{ar}-CH_3); δ_P (121.5 MHz) 45.2 ($S{=}P(Tol)_2$), -15.4 ($P(Tol)_2$; *m/z* (FAB+) 711.3 (25%, (M+H)), 465.3 (100%, (M+) - $P(Tol)_2$); Found (FAB+) 711.2431; $C_{48}H_{41}P_2S$ (M+H), requires 711.2404; $[\alpha]_D^{20}$ = - 4 ($CHCl_3$, c = 0.5). And *bis-sulphide* **446** (30 mg, 27%) as a colourless solid; Mp >300°C; R_f (10:1, petrol:EtOAc) 0.14; ν_{max} (film) 3050 (C_{ar}-H), 1599 (C=C), 1550 (C=C), 1497 (C=C), 1449 (C=C); δ_H (300 MHz) 7.74-7.69 (4H, m, 4 x C_{ar}-H), 7.62-7.48 (10H, m, 10 x C_{ar}-H), 7.34-7.29 (2H, m, 2 x C_{ar}-H), 7.03-6.97 (8H, m, 8 x C_{ar}-H), 6.80-6.70 (4H, m, 4 x C_{ar}-H), 2.34 (6H, s, 2 x C_{ar}-CH_3), 2.30 (6H, s, 2 x C_{ar}-CH_3); δ_C (75.5 MHz) 140.90 (quat., C_{ar}), 140.87 (quat., C_{ar}), 140.67 (quat., C_{ar}), 140.63 (quat., C_{ar}), 139.93 (quat., C_{ar}), 139.87 (quat., C_{ar}), 139.83 (quat., C_{ar}), 139.76 (quat., C_{ar}), 133.72 (quat., C_{ar}), 132.69 (C_{ar}-H), 132.54 (C_{ar}-H), 132.38 (quat., C_{ar}), 132.22 (C_{ar}-H), 132.08 (C_{ar}-H), 131.22 (quat., C_{ar}), 129.50 (C_{ar}-H), 129.34 (C_{ar}-H), 129.18 (quat., C_{ar}), 128.97 (quat., C_{ar}), 128.58 (C_{ar}-H), 128.45 (C_{ar}-H), 128.41 (C_{ar}-H), 128.28 (C_{ar}-H), 128.05 (quat., C_{ar}), 127.72 (C_{ar}-H), 127.61 (C_{ar}-H), 127.45 (C_{ar}-H), 127.22 (C_{ar}-H), 127.49 (C_{ar}-H), 125.64 (C_{ar}-H), 21.33 (C_{ar}-CH_3), 21.31 (C_{ar}-CH_3); δ_P (121.5 MHz) 43.9 (2 x (S=P)); *m/z* (FAB+) 743.1 (50%, (M+)), 497.1 (100%, (M+) - $P(S)Tol_2$), 465.2 ((M+) - $P(S)Tol_2$, - S); Found (FAB+) 743.2152; $C_{48}H_{41}P_2S_2$ (M+H), requires 743.2406; $[\alpha]_D^{20}$ = - 18 ($CHCl_3$, c = 0.5).

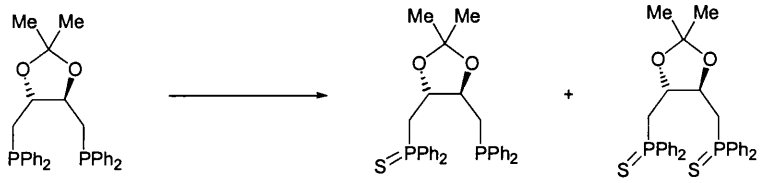
(*R*)-1-[2-(2,5-Dimethyl-phospholan-1-yl)-phenyl]-2,5-dimethyl-phospholane 1-sulphide 451 and (*R*)-1,2 *Bis*-(2,5-dimethyl-phospholane 1-sulphide)benzene 452



450 **451** **452**

Sulphur (31.4 mg, 0.979 mmol) was added to a stirring solution of (*R*)-DUPHOS **450** (250 mg, 0.816 mmol) in degassed benzene (12 mL). The resulting solution was heated to reflux for 2.5 hours before being allowed to cool to room temperature. The solvent was removed *in vacuo* and the resulting residue was purified *via* flash chromatography (gradient elution, 10:1 to 5:1, petrol:EtOAc) to yield in order of elution, to yield in order of elution, (*R*)-DUPHOS **450**, (8 mg, 3%). And *mono-sulphide* **451** (194 mg, 70%) as a colourless solid; Mp 142-143°C; R_f (5:1, petrol:EtOAc) 0.45; ν_{max} (film) 3049 (C_{ar}-H), 2949 (C-H), 2924 (C-H), 2862 (C-H), 1448 (C-C); δ_H (300 MHz) 7.69-7.66 (1H, m, C_{ar}-H), 7.41-7.39 (2H, m, 2 x C_{ar}-H), 7.32-7.31 (1H, m, C_{ar}-H), 3.04-2.98 (1H, m, (P=S)-C-H), 2.76-2.47 (4H, m), 2.13-1.89 (4H, m), 1.55-1.33 (6H, m), 1.25-1.14 (3H, m, CH_3), 0.98-0.82 (6H, m, 2 x CH_3); δ_C (75.5 MHz) 142.50 (quat., C_{ar}), 142.35 (quat., C_{ar}), 142.05 (quat., C_{ar}), 140.80 (quat., C_{ar}), 140.34 (quat., C_{ar}), 139.87 (quat., C_{ar}), 139.41 (quat., C_{ar}), 135.61 (C_{ar}-H), 135.58 (C_{ar}-H), 135.47 (C_{ar}-H), 135.43 (C_{ar}-H), 130.16 (C_{ar}-H), 130.02 (C_{ar}-H), 129.98 (C_{ar}-H), 129.89 (C_{ar}-H), 128.61 (C_{ar}-H), 128.47 (C_{ar}-H), 41.88 (C-H), 41.32 (C-H), 36.83 (CH_2), 36.81 (CH_2), 36.34 (CH_2), 36.27 (CH_2), 36.17 (CH_2), 36.02 (CH_2), 34.90 (C-H), 34.74 (C-H), 31.84 (C-H), 31.14 (C-H), 30.48 (CH_2), 30.46 (CH_2), 30.39 (CH_2), 30.22 (CH_2), 20.55 (CH_3), 19.58 (CH_3), 19.54 (CH_3), 18.03 (CH_3), 17.98 (CH_3), 13.82 (CH_3); δ_P (121.5 MHz) 72.86 (S=P), 5.72 (P(C_{alk})$_2$); *m/z* (FAB+) 339.2 (100%, (M+H)); Found (FAB+) 339.1469; $C_{18}H_{29}P_2S$ (M+H), requires 339.1465; $[\alpha]_D^{20}$ = -140 ($CHCl_3$, c = 0.5). And *bis-sulphide* **452** (53 mg, 18%) as a colourless solid; Mp 258-259°C; R_f (5:1, petrol:EtOAc) 0.25; ν_{max} (film) 3053 (C_{ar}-H), 2962 (C-H), 2925 (C-H), 1456 (C-C); δ_H (300 MHz) 7.67-7.59 (2H, m, 2 x C_{ar}-H), 7.56-7.50 (2H, m, 2 x C_{ar}-H), 3.54-3.42 (2H, m, 2 x P-C-H), 2.88-2.77 (2H, m, 2 x P-C-H), 2.59-2.43 (2H, m, 2 x C(H)-***H***), 2.16-1.95 (4H, m, 4 x C(H)-***H***), 1.50-1.38 (2H, m, 2 x C(H)-***H***), 1.34 (6H, dd, J = 16.6 and 6.8, 2 x CH_3), 0.99 (6H, dd, J = 20.0 and 7.5, 2 x CH_3); δ_C (75.5 MHz) 135.90 (quat., C_{ar}), 135.82 (quat., C_{ar}), 135.06 (quat., C_{ar}), 134.98 (quat., C_{ar}), 132.94 (C_{ar}-H), 132.81 (C_{ar}-H), 131.69 (C_{ar}-H), 130.56 (C_{ar}-H), 130.45 (C_{ar}-H), 130.40 (C_{ar}-H), 130.36 (C_{ar}-H), 130.25 (C_{ar}-H), 42.05 (C-H), 42.03 (C-H), 41.32 (C-H), 41.30 (C-H), 33.39 (C-H), 33.36 (C-H), 32.65 (C-H), 32.62 (C-H), 30.40 (C-H), 30.35 (CH_2), 30.29 (CH_2), 29.87 (CH_2), 29.80 (CH_2), 29.70 (CH_2), 29.59 (CH_2), 29.53 (CH_2), 20.60 (CH_3), 12.04 (CH_3); δ_P (121.5 MHz) 74.48 (2 x S=P); *m/z* (FAB+) 371.1 (85%, (M+H)); Found 371.1181; $C_{18}H_{29}P_2S_2$ (M+H), requires 371.1186; $[\alpha]_D^{20}$ = -44 ($CHCl_3$, c = 0.5).

(*R*)-[5-(Diphenyl-phosphinothioylmethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl-methyl]-diphenyl-phosphane 448 and (*R*)-4,5-*Bis*-(diphenyl-phosphinothioylmethyl)-2,2-dimethyl-[1,3]dioxolane 449



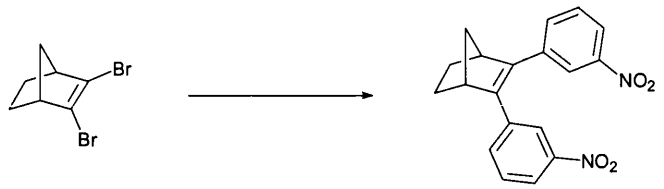
447 **448** **449**

Sulphur (6.2 mg, 0.19 mmol) was added to a stirring solution of (*R*)-DIOP **447** (80 mg, 0.16 mmol) in degassed benzene (3 mL). The resulting solution was heated to reflux for 2.5 hours before being allowed to cool to room temperature. The solvent was removed *in vacuo* and the resulting residue was purified *via* flash chromatography (gradient elution, 10:1 to 5:1, petrol:EtOAc) to yield in order of elution, (*R*)-DIOP **447** (21 mg, 26%) as a colourless solid. And *mono-sulphide* **448** (15 mg, 18%) as a colourless solid; melting point: 128-130°C; R_f (5:1, petrol:EtOAc) 0.39; ν_{max} (film) 3055 (C_{ar}-H), 2986 (C-H), 2930 (C-H), 1437 (C-C), 1102 (C-O); δ_H (300 MHz) 7.89-7.73 (4H, m, 4 x P(S)-(C_{ar}-H_{ortho})), 7.50-7.38 (10H, m, [4 x P-(C_{ar}-H_{ortho})] + [4 x P(S)-(C_{ar}-H_{meta})] + [2 x P(S)-(C_{ar}-H_{para})]), 7.33-7.30 (6H, m, [4 x P-(C_{ar}-H_{meta})] + [2 x P-(C_{ar}-H_{para})]), 4.38-4.29 (1H, m, P(S)-CH_2-C-***H***), 3.89-3.85 (1H, m, P-CH_2-C-***H***), 2.92-2.81 (1H, m, P(S)-C(H)-***H***), 2.55 (1H, m, P(S)-C(H)-***H***), 2.37-2.34 (2H, m, P-CH_2), 1.26 (3H, s, C(Me)-CH_3), 1.21 (3H, s, C(Me)-CH_3); δ_C (75.5 MHz) 138.41 (quat., C_{ar}), 133.25 (quat. C_{ar}), 129.99 (C_{ar}-H), 132.68 (C_{ar}-H), 132.43 (C_{ar}-H), 131.73 (C_{ar}-H), 131.59 (C_{ar}-H), 130.98 (C_{ar}-H), 130.84 (C_{ar}-H), 128.83 (C_{ar}-H), 128.64 (C_{ar}-H), 128.50 (C_{ar}-H), 128.47 (C_{ar}-H), 128.41 (C_{ar}-H), 128.37 (C_{ar}-H), 128.28 (C_{ar}-H), 128.11 (C_{ar}-H), 109.42 (quat., Me_2CO_2), 79.62 (C(O)-H), 79.46 (C(O)-H), 79.27 (C(O)-H), 77.20 (C(O)-H), 76.86 (C(O)-H), 76.73 (C(O)-H), 37.24 (CH_2), 36.74 (CH_2), 31.56 (CH_2), 31.36 (CH_2), 27.02 (CH_3), 26.00 (CH_3); δ_P (121.5 MHz) 40.89 (S=PPh_3), -21.66 (PPh_2); *m/z* (FAB+) 531.2 (100%, (M+H)); Found (FAB+) 531.1686; $C_{31}H_{33}O_2P_2S$ (M+H) requires 531.1677. And *bis-sulphide* **449** (20 mg, 27%) as a colourless solid; Mp 179-180°C; R_f (5:1, petrol:EtOAc) 0.25; ν_{max} (film) 3055 (C_{ar}-H), 2986 (C-H), 2934 (C-H), 1436 (C-C), 1103 (C-O); δ_H (300 MHz) 7.89-7.73 (8H, m, 8 x P(S)-(C_{ar}-H_{ortho})), 7.49-7.37 (12H, m, [8 x P(S)-(C_{ar}-H_{meta})] + [4 x P(S)-(C_{ar}-H_{para})], 4.46-4.35 (2H, m, 2 x C(O)-H), 2.94-2.84 (2H, m, 2 x P(S)-C(H)-***H***), 2.61-2.51 (2H, m, 2 x P(S)-C(H)-H), 1.11 (6H, s, $C(CH_3)_2$); δ_C (75.5 MHz) 134.39 (quat., C_{ar}) 133.36 (quat., C_{ar}) 133.30 (C_{ar}-H), 132.27 (C_{ar}-H), 132.06 (C_{ar}-H), 131.97 (C_{ar}-H), 131.92 (C_{ar}-H), 131.75 (C_{ar}-H), 131.71 (C_{ar}-H), 131.35 (C_{ar}-H), 131.18 (C_{ar}-H), 131.04 (C_{ar}-H), 129.16 (C_{ar}-H), 129.00 (C_{ar}-H), 128.67 (C_{ar}-H), 128.50 (C_{ar}-H), 109.80 (quat., Me_2CO_2), 77.83 (CH_2), 77.63 (CH_2), 76.79 (CH_2), 76.76 (CH_2), 76.61 (CH_2), 36.43 (CH_2), 35.68 (CH_2), 27.16 (CH_3); δ_P (121.5 MHz) 41.29 (2 x S=PPh_2); *m/z* (FAB+) 563.2 (100%, (M+H)), 531.2 ((M+H) - S); Found (FAB+) 563.1405; $C_{31}H_{33}O_2P_2S_2$ (M+H), requires 653.1397.

Palladium Chemistry : Suzuki -Miyaura couplings

Suzuki chemistry of norbornene Dibromide 380

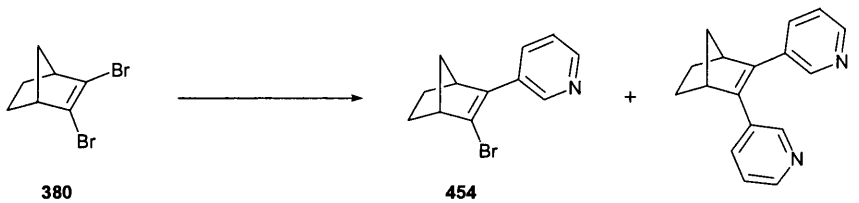
2,3-*Bis*-(3-nitro-phenyl)-bicyclo[2.2.1]hept-2-ene 463



380 **463**

Na_2CO_3 (0.6 mL, 2M solution, 1.2 mmol) was added to a solution of $Pd(PPh_3)_4$ (46 mg, 0.0397 mmol), dibromoalkene **380** (100 mg, 0.397 mmol) and 3-nitro benzene boronic acid **460** (79 mg, 0.476 mmol) in degassed DME (4 mL) in a sealed tube. The reaction was then heated to 90°C for one hour. The reaction mixture was then allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was taken up in EtOAc (20 mL) and washed with water (2 x 10 mL). The organic layer was then dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol-10:1, petrol:EtOAc) to yield, *dinitro* **463** (80 mg, 60%) as a yellow solid; Mp 114.5-115.5°C; R_f (5:1, Petrol:EtOAc) 0.49; ν_{max} (film) 3082 (C_{ar}-H), 2967 (C-H), 2870 (C-H), 1527 (NO_2), 1350 (NO_2); δ_H (300 MHz) 8.07-8.04 (2H, m, 2 x C_{ar}-H), 7.47-7.43 (2H, m, C_{ar}-H), 7.40-7.35 (2H, m, C_{ar}-H), 3.35 (2H, app. t, J = 1.5, 2 x C_{brid}-H), 2.01-1.97 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.88-1.85 (1H, m, C(H)-***H***), 1.46-1.39 (3H, m, H_{endo}-C(H)-C(H)-H_{endo} + C(H)-***H***); δ_C (75.5 MHz) 148.3 (quat., C_{ar}-NO_2), 142.3 (quat., C), 137.58 (quat., C), 133.5 (C_{ar}-H), 129.2 (C_{ar}-H), 122.2 (C_{ar}-H), 121.8 (C_{ar}-H), 48.7 (2 x C_{brid}-H), 47.2 (C_{brid}-CH_2-C_{brid}), 25.8 (2 x CH_2); *m/z* (FAB+) 336.1 (100%, (M+)); Found 336.1109; $C_{19}H_{16}N_2O_4$ (M+) requires 336.1110.

3-(3-Bromo-bicyclo[2.2.1]hept-2-en-2-yl)-pyridine 454 and 3-(3-(3-pyridyl)-bicyclo[2.2.1]hept-2-en-2-yl)-pyridine 455

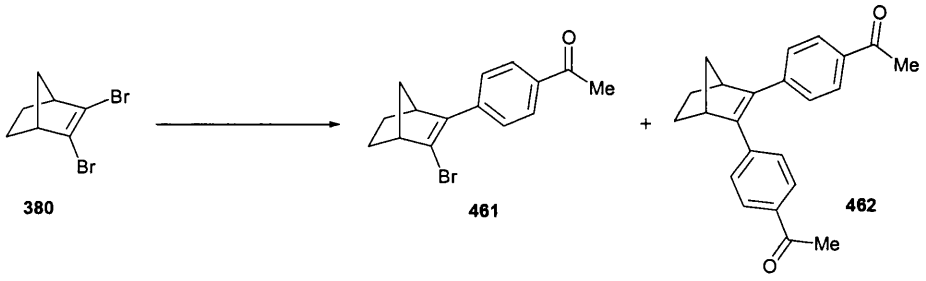


380 **454** **455**

Na_2CO_3 (0.6 mL, 2M solution, 1.2 mmol) was added to a solution of $Pd(PPh_3)_4$ (46 mg, 0.0397 mmol), dibromoalkene **380** (100 mg, 0.397 mmol) and boronic ester (78 mg, 0.476 mmol) in degassed DME (4mL) in a sealed tube. The reaction was heated to 90°C for one hour. The reaction mixture was then allowed to return to room temperature and the solvent removed *in vacuo*. The residue was taken up in EtOAc (20mL) and washed with water (2 x 10 mL). The organic layer was then dried (Na_2SO_4) and then concentrated *in*

vacuo. The residue was purified *via* flash chromatography (gradient elution, 5:1, petrol: EtOAc, - EtOAc) to yield *mono pyridine* **454** (35mg, 35%) as a colourless oil; R_f (EtOAc) 0.87; ν_{max} (film) 1600 (C=C), 1578, (C=C), 1562 (C=C), 1529; δ_H (300 MHz) 8.82 (1H, s, (quat.C_{ar}-(C_{ar}-H)-N), 8.47 (1H, d, J = 3.7, N-(C_{ar}-***H***)-C_{ar}(H)), 7.96 (1H, app. dt, J = 8.0 and 1.9, N-C_{ar}(H)-C_{ar}(H)-C_{ar}-***H***), 7.28-7.24 (1H, m, N-C_{ar}-H), 3.32-3.30 (1H, m, C_{brid}-H), 3.10-3.08 (1H, m, C_{brid}-H), 2.04-1.75 (3H, m, H_{exo}-C(H)-C(H)-H_{exo} + C(H)-***H***), 1.40-1.38 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}), 1.31-1.29 (1H, d, J = 8.5, C(H)-***H***); δ_C (90.5 MHz) 147.8 (C), 147.3 (C_{ar}), 140.3 (quat., C), 133.2 (C_{ar}), 130.3 (quat., C), 122.9 (quat., C) ,122.8 (C_{ar}), 53.1 (C_{brid}), 46.8 (C_{brid}), 46.5 (C_{brid}-***C***H_2-C_{brid}), 26.1 (CH_2), 25.9 (CH_2); *m/z* (CI+) 252.1/250.1, (85%, (M+H)), 188.1 ((M+NH_4) - Br), 172.1 (100%, (M+H) - Br); Found (ES+) 250.0230; $C_{12}H_{13}{}^{79}BrN$ (M+H), requires 250.0231. And *bis pyridine* **455** (30 mg, 30%) as a colourless oil; R_f (EtOAc) 0.11; ν_{max} (film) 1581 (C=C), 1561 (C=C); δ_H (360 MHz) 8.46 (2H, d, J = 1.7, 2 x C_{ar}-H), 8.42 (2H, dd, J = 3.3 and 1.5, 2 x C_{ar}-H), 7.47 (2H, dt, J = 8.0 and 1.9, 2 x C_{ar}-H), 7.17-7.13 (2H, m, 2 x C_{ar}-H), 3.29 (2H, s, 2 x C_{brid}-H), 1.96-1.91 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.83 (1H, app. dt, J = 8.5 and 2.0, C(H)-***H***), 1.44-1.38 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}), 1.36 (1H, app. d, J = 7.3, C(H)-***H***); δ_C (90.5 MHz) 150.5 (C_{ar}-H), 149.8 (C_{ar}-H), 142.7 (C_{ar}-H), 136.6 (quat., C), 134.0 (C_{ar}-H), 125.1 (quat., C), 50.4 (C_{brid}-***C***H_2-C_{brid}), 49.2 (2 x C_{brid}-H), 27.7 (2 x *C*H_2); *m/z* (CI+) 249.2 (100%, (M+H)); Found (ES+) 249.1393; $C_{17}H_{17}N_2$ (M+H), requires 249.1391.

2-(4-acetyl-phenyl)-3-bromo-bicyclo[2.2.1]hept-2-ene 461 and
2,3-*Bis*(4-acetyl-phenyl)-bicyclo[2.2.1]hept-2-ene 462



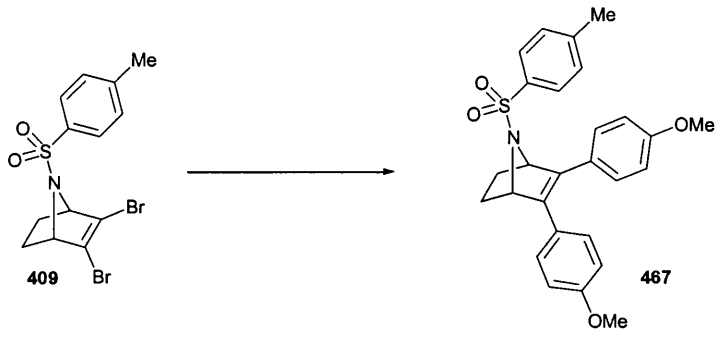
Na_2CO_3 (0.6 mL, 2M solution, 1.2 mmol) was added to a solution of $Pd(PPh_3)_4$ (46 mg, 0.0397 mmol), dibromoalkene **380** (100 mg, 0.397 mmol) and 4-acetyl benzene boronic acid **459** (78 mg, 0.0476 mmol) in degassed DME (4mL) in a sealed tube. The reaction was then heated to 90°C for one hour. The reaction mixture was then cooled to room temperature and the solvent removed *in vacuo*. The residue was taken up in EtOAc (20mL) and washed with water (2 x 10 mL). The organic layer was then dried (Na_2SO_4) and the concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol-10:1, petrol:EtOAc) to yield, in order of elution; *aryl vinyl bromide* **461** (10 mg, 9%) as a colourless oil; R_f (5:1, petrol:EtOAc) 0.61; ν_{max} (film) 1684 (C=O), 1603 (C=C); δ_H (300 MHz) 7.98-7.91 (2H, m, Ac-C_{ar}-(C_{ar}-H)$_2$), 7.71-7.67 (2H, m, C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 3.34-3.32 (1H, m, C_{brid}-H), 3.12-3.10 (1H, m, C_{brid}-H), 2.59 (3H, s, OCH_3), 1.88-1.83 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.78-1.74 (1H, m, C_{brid}-C(H)-***H***), 1.42-1.39 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}), 1.31-1.25 (1H, m, C_{brid}-C(H)-***H***), δ_C (75.5 MHz) 197.6 (quat., C=O), 142.7 (quat., C), 139.6 (quat., C), 128.7 (quat., C), 128.3 (Ac-C_{ar}-(***C***$_{ar}$-H)$_2$), 126.4 (C_{vin}-C_{ar}-(***C***$_{ar}$-H)$_2$), 123.7 (quat., C_{vin}-Br), 53.7, 47.4,

46.5, 26.6, 26.4, 26.2; *m/z* (CI+) 310.1/308.1 (65%, $(M+NH_4)$), 293.1/291.1 (50%, (M+H)), 230.2 ($(M+NH_4)$ - Br), 213.1 (100%, (M+H) - Br); Found (ES+) 291.0381; $C_{15}H_{16}{}^{79}BrO$ requires 291.0384. And *bis aryl* **462** (51 mg, 39%) as a pale yellow oil; R_f (5:1, petrol:EtOAc) 0.52; ν_{max} (film) 1681 (C=O), 1600 (C=C); δ_H (400 MHz) 7.84-7.80 (4H, m, 2 x Ac-C_{ar}-(C_{ar}-H)$_2$), 7.30-7.22 (4H, m, 2 x C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 3.31 (2H, t, J = 1.6, 2 x C_{brid}-H), 2.57 (6H, s, 2 x C(O)-CH_3), 1.95-1.90 (2H, m, ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.86-1.80 (1H, m, C(H)-***H***), 1.47-1.40 (2H, m, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$), 1.36-1.33 (1H, m, C(H)-***H***); δ_C (100.5 MHz) 197.2 (quat., 2 x C=O), 143.3 (quat., 2 x C_{ar}), 141.4 (quat., 2 x C), 135.3 (quat., 2 x C), 128.3 (2 x C_{ar}-H), 127.7 (2 x C_{ar}-H), 62.1, 48.9, 47.2, 26.6; *m/z* (EI+) 330.1 (40%, (M+)), 302.1 ((M+) - CH_2=CH_2), 287.1, ((M+) - Ac)); (CI+) 348.3 (100%, $(M+NH_4)$), 331.2 (30%, (M+H)); Found (ES+) 331.1698; $C_{23}H_{23}O_2$ (M+H), requires 331.1698.

The enantiomers of **461** were separated by HPLC using a Chiralcel OD® column (90:10, hexane:*iso*propanol), 1 mL/min; t_r = 12.0 min and 13.2 min.

Suzuki chemistry of tosyl dibromide ***409***

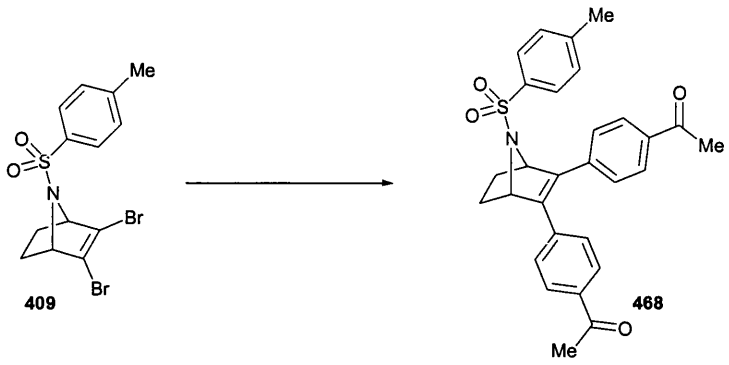
2,3-*Bis*-(4-methoxy-phenyl)-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 467



Na_2CO_3 (0.37 mL, 2M solution, 0.738 mmol) was added to a solution of $Pd_2(dba)_3$ (11.3 mg, 0.012 mmol), triphenylphosphine (13 mg, 0.0492 mmol), dibromoalkene **409** (100 mg, 0.246 mmol) and 4-methoxy benzene boronic acid **457** (75 mg, 0.492 mmol) in degassed DME (4mL) in a sealed tube. The reaction was then heated to 90°C for one hour. The reaction mixture was then cooled and the solvent removed *in vacuo*. The residue was taken up in EtOAc (20mL) and washed with water (2 x 10 mL). The organic layer was then dried (Na_2SO_4) and then concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (gradient elution, petrol to 3:1, petrol:EtOAc) to yield *biaryl* **467** (47 mg, 41%) as a pale yellow solid; Mp 156-157°C; R_f (2:1, petrol:EtOAc) 0.57; ν_{max} (film) 1603 (C=C), 1572 (C=C), 1515 (C=C), 1506 (C=C), 1339 (SO_2), 1157 (SO_2); δ_H (300 MHz) 7.58-7.56 (2H, m, SO_2-C_{ar}-(C_{ar}-H)$_2$), 6.98 (2H, d, J = 8.0, Me-C_{ar}-(C_{ar}-H)$_2$), 6.84-6.79 (4H, m, 2 x C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 6.70-6.66 (4H, m, 2 x MeO-C_{ar}-(C_{ar}-H)$_2$), 4.88-4.87 (2H, m, 2 x C_{brid}-H), 3.78 (6H, s, 2 x C_{ar}-OCH_3), 2.25-2.23 (5H, m, C_{ar}-CH_3 + ***H***$_{exo}$-C(H)-C(H)-***H***$_{exo}$), 1.47-1.42 (2H, m, ***H***$_{endo}$-C(H)-C(H)-***H***$_{endo}$); δ_C (75.5 MHz) 158.7 (quat, 2 x C_{ar}-OMe), 142.6 (quat., C), 136.6 (quat., C), 135.9 (quat., C), 129.2 (2 x C_{ar}-H), 128.3 (2 x C_{vin}-C_{ar}-(***C***$_{ar}$-H)$_2$), 127.8 (2 x C_{ar}-H), 125.7 (quat., 2 x C_{vin}-C_{ar}), 113.3 (2 x MeO-C_{ar}-(***C***$_{ar}$-H)$_2$), 67.0 (2 x C_{brid}-H), 54.9 (2 x C_{ar}-OCH_3), 26.7 (2 x CH_2), 21.2 (C_{ar}-***C***H_3); *m/z*

(FAB+) 462.2 (70%, (M+H)), 433.1 (100%, ((M+) - CH_2=CH_2); Found (FAB+) 462.1743; $C_{27}H_{28}NO_4S$ (M+H), requires 462.1739.

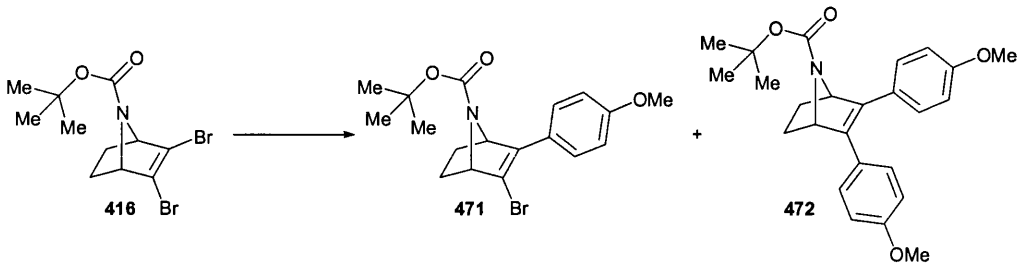
2,3-*Bis*(4-acetyl-phenyl)-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene 468



Na_2CO_3 (2 M solution, 0.37 mL, 0.738 mmol) was added to a solution of $Pd_2(dba)_3$ (11.3 mg, 0.012 mmol), triphenylphosphine (13 mg, 0.0492 mmol), dibromoalkene **409** (100 mg, 0.246 mmol) and 4-acetyl benzene boronic acid **459** (75 mg, 0.492 mmol) in degassed DME (4mL) in a sealed tube. The reaction was then heated to 90°C for one hour. The reaction mixture was then allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was taken up in EtOAc (20 mL) and washed with water (2 x 10 mL). The organic layer was dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was purified *via* flash chromatography (gradient elution, petrol to 3:1, petrol:EtOAc) to yield *diketone* **468** (45 mg, 38%) as a pale yellow oil; R_f (2:1, petrol:EtOAc) 0.52; δ_H (300 MHz) 7.78-7.74 (4H, m, 2 x Ac-C_{ar}(-C_{ar}-H)$_2$), 7.61-7.58 (2H, m, SO_2-C_{ar}-(C_{ar}-H)$_2$), 7.03-7.01 (2H, d, J = 8.0, Me-C_{ar}-(C_{ar}-H)$_2$), 6.98-6.95 (4H, m, 2 x C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 5.00-4.99 (2H, m, 2 x C_{brid}-H), 2.58 (6H, s, 2 x C(O)CH_3), 2.35-2.32 (2H, m, $\boldsymbol{H}_{exo}$-C(H)-C(H)-$\boldsymbol{H}_{exo}$), 2.28 (3H, s, C_{ar}-CH_3), 1.52-1.47 (2H, m, $\boldsymbol{H}_{endo}$-C(H)-C(H)-$\boldsymbol{H}_{endo}$); δ_C (75.5 MHz) 197.2 (quat., 2 x C=O), 143.4 (quat., Me-C_{ar}), 140.2 (quat., C), 137.5 (quat., C), 136.4 (quat., C), 135.9 (quat., C), 129.7 (Me-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 128.4 (2 x Ac-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 127.9 (SO_2-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 127.4 (2 x C_{vin}-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 67.1 (2 x C_{brid}-H), 26.6 (2 x CH_2), 26.5 (2 x C(O)$\boldsymbol{C}H_3$), 21.4 (C_{ar}-$\boldsymbol{C}H_3$);

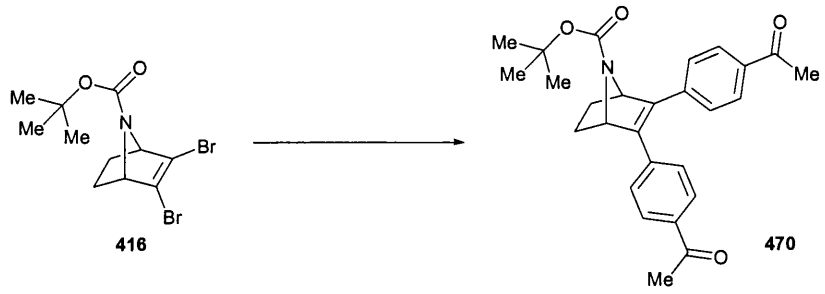
Suzuki chemistry of BOC dibromide **416**

2-Bromo-3-(4-methoxy-phenyl)-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 471 and 2,3-*Bis*-(4-methoxy-phenyl)-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 472



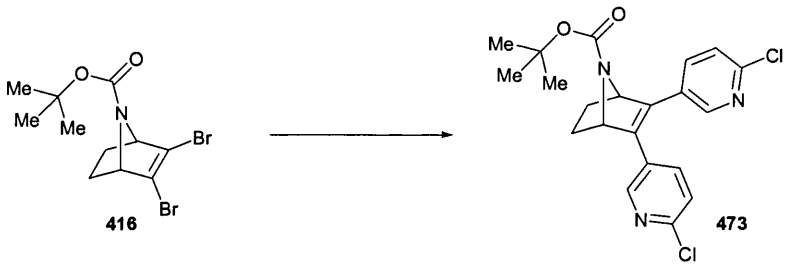
Na_2CO_3 (2 M, 0.43 mL, 0.85 mmol) was added to a solution of $Pd_2(dba)_3$ (13 mg, 0.014 mmol), PPh_3 (15 mg, 0.057 mmol), 4-methoxy benzene boronic acid **457** (136 mg, 0.566 mmol) and dibromide **416** (100 mg, 0.283 mmol) in degassed DME (3.5mL) and the reaction mixture was then heated to 90°C in a sealed tube for one hour. After cooling to room temperature, EtOAc (20 mL) was added and the reaction mixture washed with water (3 x 5 mL). The organic layer was then dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The solid residue was purified *via* flash chromatography (gradient elution, 20:1 to 5:1, petrol:EtOAc) to yield, in order of elution; *mono anisole* **471** (13 mg, 12%) as a yellow oil; R_f (5:1, petrol:EtOAc) 0.42; ν_{max} (film) 1704 (C=O); δ_H (300MHz) 7.61-7.58 (2H, m, C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 6.93-6.90 (2H, m, MeO-C_{ar}-(C_{ar}-H)$_2$), 5.00 (1H, br s, C_{brid}-H), 4.67 (1H, br s, C_{brid}-H), 3.82 (3H, s, OCH_3), 2.03-1.99 (2H, m, $\boldsymbol{H}_{exo}$-C(H)-C(H)-$\boldsymbol{H}_{exo}$), 1.54-1.48 (1H, m, C(H)-$\boldsymbol{H}_{endo}$), 1.43 (9H, s, $C(CH_3)_3$), 1.39-1.36 (1H, m, C(H)-$\boldsymbol{H}_{endo}$); *m/z* (FAB+) 381.1/379.1 (10%, (M+)), 353.1/351.1 ((M+) - CH_2=CH_2), 326.0/324.0 ((M+H) - ^{t}Bu), 297.0/295.0 ((M+) - ^{t}Bu, - CH_2=CH_2), 281.1/279.1 ((M+) - $CO_2{}^t$Bu), 253.1/251.1 ((M+) - $CO_2{}^t$Bu, - CH_2=CH_2); Found (FAB+) 381.0757; $C_{18}H_{22}{}^{81}BrNO_3$ (M+), requires 381.0763. And *bis anisole* **472** (73 mg, 63%) as a yellow oil; R_f (5:1, petrol:EtOAc) 0.32; ν_{max} (film) 1703 (C=O); δ_H (300 MHz) 7.21 (4H, d, J = 8.6, 2 x C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 6.80 (4H, d, J = 8.6, 2 x MeO-C_{ar}-(C_{ar}-H)$_2$), 4.91 (2H, br s, 2 x C_{brid}-H), 3.79 (6H, s, 2 x OCH_3), 2.08-2.04 (2H, m, $\boldsymbol{H}_{exo}$-C(H)-C(H)-$\boldsymbol{H}_{exo}$), 1.51-1.48 (2H, m, $\boldsymbol{H}_{endo}$-C(H)-C(H)-$\boldsymbol{H}_{endo}$), 1.44 (9H, s, $C(CH_3)_3$; δ_C (75.5 MHz) 158.5 (quat., 2 x C_{ar}-OMe), 155.4 (quat., C=O), 139.5 (quat., br, 2 x C_{vin}), 128.5 (2 x C_{vin}-C_{ar}-($\boldsymbol{C}_{ar}$-H)$_2$), 126.6 (quat., 2 x C_{vin}-$\boldsymbol{C}_{ar}$), 113.6 (2 x MeO-C_{ar}-(C_{ar}-H)$_2$), 79.7 (quat., C(Me)$_3$), 64.9 (2 x C_{brid}-H), 54.9 (2 x C_{ar}-O$\boldsymbol{C}H_3$), 28.0 (C($\boldsymbol{C}H_3$)$_3$), 25.2 (2 x CH_2); *m/z* (CI+) 408.1 (50%, (M+H)), 379.0 ((M+) - CH_2=CH_2), 369.1 ((M+NH_4) - ^{t}Bu), 352.0 (100%, (M+H) - ^{t}Bu), 323.0 ((M+H) - CH_2=CH_2, - ^{t}Bu), 308.0 ((M+H) - $CO_2{}^t$Bu), 293.0 ((M+NH_4) - $CO_2{}^t$Bu, - CH_2=CH_2), 279.0 ((M+H) - $CO_2{}^t$Bu, - CH_2=CH_2); Found (ES+) 408.2172; $C_{25}H_{30}NO_4$ (M+H), requires 408.2175.

2,3-*Bis*-(4-acetyl-phenyl)-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 470



Na_2CO_3 (2 M, 0.43 mL, 0.85 mmol) was added to a solution of $Pd_2(dba)_3$ (13 mg, 0.014 mmol), PPh_3 (15 mg, 0.057 mmol), 4-acetyl benzene boronic acid **459** (94 mg, 0.566 mmol) and dibromide **416** (100 mg, 0.283 mmol) in degassed DME (3 mL) and the reaction mixture was then heated to 90°C in a sealed tube for one hour. On cooling to room temperature, EtOAc (20 mL) was added and the reaction mixture was washed with water (3 x 5 mL). The organic layer was then dried (Na_2SO_4) filtered and the solvent removed *in vacuo*. The solid residue was purified *via* flash chromatography (gradient elution, 20:1 to 5:1, petrol:EtOAc) to yield *bis ketone* **470** (76 mg, 69%) as a pale yellow oil; ν_{max} (film), 1705 (C=O), 1684 (C=O); δ_H (300 MHz) 7.79 (4H, d, J = 8.3, 2 x Ac-C_{ar}-(C_{ar}-H)$_2$), 7.25 (4H, d, J = 8.3, 2 x C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 4.94 (2H, br s, 2 x C_{brid}-H), 2.51 (6H, s, 2 x C(O)CH_3), 2.08 (2H, app. br d, J = 7.9, H_{exo}-C(H)-C(H)-H_{exo}), 1.45 (2H, app. br d, J = 7.5, H_{endo}-C(H)-C(H)-H_{endo}), 1.36 (9H, s, C(CH_3)$_3$); δ_C (75.5 MHz) 197.3 (quat., 2 x (MeO)C=O), 155.5 (quat., (^{t}BuO)C=O), 142.8 (quat., 2 x C_{vin}), 138.5 (quat., 2 x C_{ar}), 136.1 (quat. 2 x C_{ar}), 128.6 (2 x Ac-C_{ar}-(C_{ar}-H)$_2$), 127.6 (2 x C_{vin}-C_{ar}-(C_{ar}-H)$_2$), 80.4 (quat., C(Me)$_3$), 65.4 (2 x C_{brid}-H), 28.1 (C(CH_3), 26.5 (C(O)CH_3), 25.5 (2 x CH_2); *m/z* (CI+) 432.0 (50%, (M+H)), 393.1 ((M+NH_4) - ^{t}Bu), 376.0 ((M+H) - ^{t}Bu), 332.0 (100%, (M+H) - $CO_2{}^t$Bu); Found (ES+) 432.2174, $C_{27}H_{30}NO_4$ (M+H), requires 432.2175.

2,3-*Bis*-(6-chloro-pyridin-3-yl)-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 473

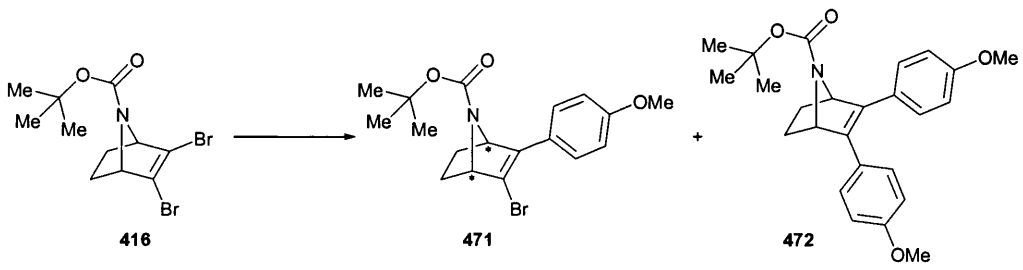


Na_2CO_3 (2 M, 0.43 mL, 0.85 mmol) was added to a solution of $Pd_2(dba)_3$ (13 mg, 0.014 mmol), PPh_3 (15 mg, 0.057 mmol), boronic ester **435** (136 mg, 0.566 mmol) and dibromide **416** (100 mg, 0.283 mmol) in degassed DME (3.5 mL) and the reaction mixture was then heated to 90°C in a sealed tube for one hour. On cooling to room temperature, EtOAc (20 mL) was added and the reaction mixture washed with water (3 x 5 mL). The organic layer was then dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The solid residue was purified *via* flash chromatography (gradient elution, 15:1 to 5:1, petrol:EtOAc) to yield *bis chloro-*

pyridine **473** (84 mg, 71%) as a pale yellow solid; Mp darkens above 105°C, melts and decomposes at 142-143°C; R_f (5:1, petrol:EtOAc) 0.38; δ_H (300 MHz) 8.17 (2H, d, J = 2.2, 2 x N-C_{ar}-H), 7.42-7.40 (2H, m, 2 x C_{ar}(Cl)-C_{ar}(H)-C_{ar}-***H***), 7.20 (2H, d, J = 8.3, 2 x C_{ar}(Cl)-C_{ar}-H), 4.89 (2H, br s, 2 x C_{brid}-H), 2.11-2.08 (2H, m, H_{exo}-C(H)-C(H)-H_{exo}), 1.43-1.39 (2H, m, H_{endo}-C(H)-C(H)-H_{endo}), 1.36 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz) 155.4 (quat., C=O), 150.8 (quat., 2 x C_{ar}-Cl), 148.0 (2 x N-C_{ar}-H), 139.5 (quat., 2 x C_{vin}), 137.0 (2 x C_{vin}-C_{ar}-(C_{ar}-H)-C_{ar}(H)), 129.2 (quat., 2 x C_{vin}-C_{ar}), 124.6 (2 x C_{ar}(Cl)-C_{ar}-H), 80.9 ($C(Me)_3$), 65.1 (2 x C_{brid}-H), 28.1 ($C(CH_3)_3$), 25.3 (2 x CH_2); *m/z* (CI+) 418.1 (20%, (M+H)), 362.1 ((M+H) - ^{t}Bu), 334.0 ((M+H) - ^{t}Bu, - CH_2=CH_2); Found (FAB+) 418.1096; $C_{21}H_{22}N_3O_2{}^{35}Cl_2$ (M+H), requires 418.1089.

Enantioselective Suzuki-Miyaura cross coupling

2-Bromo-3-(4-methoxy-phenyl)-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 471 and 2,3-*Bis*-(4-methoxy-phenyl)-7-aza-bicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester 472



General procedure for the screening of chiral ligands:

Freshly prepared Na_2CO_3 (2M, 0.212 mL, 0.425 mmol) was added to a solution of dibromide **416** (50 mg, 0.142 mmol), 4-methoxybenzene boronic acid **457** (43 mg, 0.283 mmol), $Pd_2(dba)_3$ (6.5 mg, 0.0071 mmol) and enantiopure ligand (1 eq = 0.142 mmol or 2 eq = 0.283 mmol) in degassed DME (2 mL). The reaction mixture was then heated to 80°C for 1.5 hours before being allowed to cool to room temperature. EtOAc (10 mL) was added and the reaction washed with water (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The solid residue was purified *via* flash chromatography (gradient elution, 20:1 to 5:1, petrol:EtOAc) to yield purified products. Data as above and results of the screen are on Table 1 in Chapter 3.

The enantiomers of **471** were separated by HPLC using either:

1: Chiralcel OD® column (99:1, hexane: *iso*propyl alcohol), 1 mL/min, t_r = 6.3 min and 7.3 min

2: Chiralcel AD® column (98:2, hexane: *iso*propyl alcohol), 1 mL/min, t_r = 8.8 min and 10.1 min

For identification, the first enantiomer eluted from the column was designated the (-)- enantiomer and the second the (+)-enantiomer. However this designation was only relative as the actual rotations were not measured.

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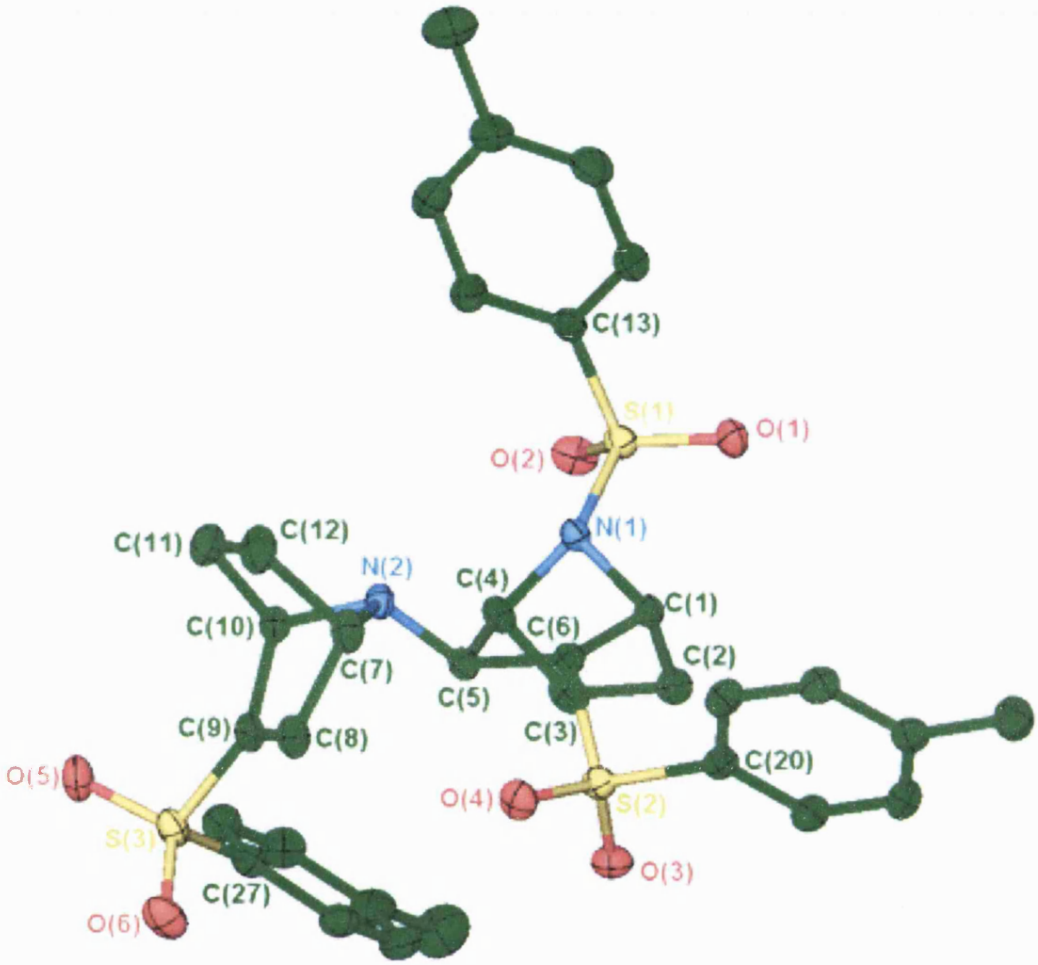
Appendix A

Crystal structure and data of dimer **396**



3,7,2'-Tris-(toluene-4-sulphonyl)-[2,7']bi[7-aza-bicyclo[2.2.1]heptyl]-2'-ene

Table 1 - Crystal data and structure refinement for dimer **396**

Identification code	dimer **396**
Empirical formula	$C_{33}H_{36}N_2O_6S_3$
Formula weight	652.82
Temperature	293(2) K
Wavelength	0.71070 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 29.8410(3) Å α = 90°
	b = 8.22200(10) Å β = 110.1400(4)°
	c = 28.0320(4) Å γ = 90°
Volume	6457.18(14) Å^3
Z	8
Density (calculated)	1.343 Mg/m^3
Absorption coefficient	0.277 mm^{-1}
F(000)	2752
Crystal size	0.30 x 0.25 x 0.20 mm
Theta range for data collection	2.93 to 27.49°.
Index ranges	0<=h<=38; -10<=k<=10; -36<=l<=34

Reflections collected	35770
Independent reflections	7359 [R(int) = 0.0335]
Reflections observed (>2σ)	5869
Max. and min. transmission	0.9468 and 0.9216
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7359 / 0 / 401
Goodness-of-fit on F^2	0.991
Final R indices [I>2σ(I)]	R_1 = 0.0380 wR_2 = 0.0968
R indices (all data)	R_1 = 0.0520 wR_2 = 0.1050
Largest diff. peak and hole	0.323 and -0.320 eÅ^{-3}

Table 2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for dimer **396**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
S(1)	857(1)	6352(1)	634(1)	40(1)
S(2)	185(1)	1314(1)	1493(1)	39(1)
S(3)	1839(1)	2233(1)	3251(1)	45(1)
O(1)	410(1)	6464(2)	227(1)	53(1)
O(2)	1036(1)	7737(1)	951(1)	57(1)
O(3)	-14(1)	2303(2)	1791(1)	50(1)
O(4)	455(1)	-94(1)	1729(1)	52(1)
O(5)	2332(1)	2706(2)	3462(1)	60(1)
O(6)	1671(1)	934(2)	3487(1)	65(1)
N(1)	830(1)	4803(2)	996(1)	36(1)
N(2)	1456(1)	2466(2)	1749(1)	40(1)
C(1)	364(1)	4008(2)	932(1)	36(1)
C(2)	127(1)	5202(2)	1188(1)	46(1)
C(3)	551(1)	5816(2)	1642(1)	51(1)
C(4)	982(1)	5001(2)	1559(1)	40(1)
C(5)	1000(1)	3206(2)	1715(1)	35(1)
C(6)	574(1)	2502(2)	1266(1)	35(1)
C(7)	1501(1)	676(2)	1827(1)	48(1)
C(8)	1506(1)	457(2)	2365(1)	48(1)
C(9)	1712(1)	1788(2)	2613(1)	43(1)
C(10)	1842(1)	2861(2)	2236(1)	43(1)
C(11)	2267(1)	2009(3)	2142(1)	62(1)
C(12)	2024(1)	466(3)	1853(1)	67(1)
C(13)	1293(1)	5778(2)	375(1)	42(1)
C(14)	1156(1)	5125(2)	-109(1)	53(1)
C(15)	1503(1)	4766(3)	-318(1)	65(1)
C(16)	1980(1)	5029(3)	-51(1)	68(1)
C(17)	2105(1)	5655(4)	432(1)	76(1)
C(18)	1768(1)	6041(3)	648(1)	62(1)
C(19)	2355(1)	4670(5)	-286(1)	108(1)
C(20)	-279(1)	697(2)	937(1)	39(1)
C(21)	-179(1)	-419(2)	616(1)	47(1)
C(22)	-544(1)	-947(2)	192(1)	51(1)
C(23)	-1006(1)	-388(2)	78(1)	48(1)
C(24)	-1095(1)	725(2)	406(1)	53(1)
C(25)	-736(1)	1279(2)	832(1)	49(1)
C(26)	-1401(1)	-954(3)	-392(1)	64(1)
C(27)	1487(1)	3967(2)	3223(1)	43(1)
C(28)	1698(1)	5495(2)	3313(1)	52(1)
C(29)	1418(1)	6850(2)	3282(1)	59(1)
C(30)	928(1)	6728(3)	3150(1)	59(1)
C(31)	722(1)	5186(2)	3058(1)	55(1)
C(32)	996(1)	3811(2)	3093(1)	50(1)
C(33)	622(1)	8222(3)	3103(1)	94(1)

Table 3 - Bond lengths [Å] and angles [°] for dimer **396**

S(1)-O(2)	1.4295(13)	S(1)-O(1)	1.4299(12)
S(1)-N(1)	1.6472(13)	S(1)-C(13)	1.7574(17)
S(2)-O(3)	1.4338(12)	S(2)-O(4)	1.4364(12)
S(2)-C(20)	1.7641(16)	S(2)-C(6)	1.7937(15)
S(3)-O(6)	1.4348(13)	S(3)-O(5)	1.4378(13)
S(3)-C(9)	1.7350(17)	S(3)-C(27)	1.7576(18)
N(1)-C(1)	1.4904(19)	N(1)-C(4)	1.4938(19)
N(2)-C(5)	1.4651(19)	N(2)-C(10)	1.4876(19)
N(2)-C(7)	1.487(2)	C(1)-C(2)	1.526(2)
C(1)-C(6)	1.549(2)	C(1)-H(1)	0.9800
C(2)-C(3)	1.538(3)	C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700	C(3)-C(4)	1.537(2)
C(3)-H(3A)	0.9700	C(3)-H(3B)	0.9700
C(4)-C(5)	1.536(2)	C(4)-H(4)	0.9800
C(5)-C(6)	1.560(2)	C(5)-H(5)	0.9800
C(6)-H(6)	0.9800	C(7)-C(8)	1.514(3)
C(7)-C(12)	1.548(3)	C(7)-H(7)	0.9800
C(8)-C(9)	1.328(2)	C(8)-H(8)	0.9300
C(9)-C(10)	1.528(2)	C(10)-C(11)	1.549(2)
C(10)-H(10)	0.9800	C(11)-C(12)	1.545(3)
C(11)-H(11A)	0.9700	C(11)-H(11B)	0.9700
C(12)-H(12A)	0.9700	C(12)-H(12B)	0.9700
C(13)-C(18)	1.376(2)	C(13)-C(14)	1.383(2)
C(14)-C(15)	1.385(3)	C(14)-H(14)	0.9300
C(15)-C(16)	1.379(3)	C(15)-H(15)	0.9300
C(16)-C(17)	1.374(3)	C(16)-C(19)	1.511(3)
C(17)-C(18)	1.379(3)	C(17)-H(17)	0.9300
C(18)-H(18)	0.9300	C(19)-H(19A)	0.9600
C(19)-H(19B)	0.9600	C(19)-H(19C)	0.9600
C(20)-C(25)	1.379(2)	C(20)-C(21)	1.387(2)
C(21)-C(22)	1.378(3)	C(21)-H(21)	0.9300
C(22)-C(23)	1.382(2)	C(22)-H(22)	0.9300
C(23)-C(24)	1.387(3)	C(23)-C(26)	1.509(3)
C(24)-C(25)	1.379(3)	C(24)-H(24)	0.9300
C(25)-H(25)	0.9300	C(26)-H(26A)	0.9600
C(26)-H(26B)	0.9600	C(26)-H(26C)	0.9600
C(27)-C(32)	1.388(2)	C(27)-C(28)	1.389(2)
C(28)-C(29)	1.378(3)	C(28)-H(28)	0.9300
C(29)-C(30)	1.384(3)	C(29)-H(29)	0.9300
C(30)-C(31)	1.394(3)	C(30)-C(33)	1.508(3)
C(31)-C(32)	1.379(3)	C(31)-H(31)	0.9300
C(32)-H(32)	0.9300	C(33)-H(33A)	0.9600
C(33)-H(33B)	0.9600	C(33)-H(33C)	0.9600
O(2)-S(1)-O(1)	119.37(8)	O(2)-S(1)-N(1)	108.68(7)
O(1)-S(1)-N(1)	108.10(7)	O(2)-S(1)-C(13)	107.47(8)
O(1)-S(1)-C(13)	107.93(8)	N(1)-S(1)-C(13)	104.29(7)
O(3)-S(2)-O(4)	117.92(8)	O(3)-S(2)-C(20)	108.78(7)
O(4)-S(2)-C(20)	108.73(7)	O(3)-S(2)-C(6)	110.28(7)
O(4)-S(2)-C(6)	105.81(7)	C(20)-S(2)-C(6)	104.48(7)
O(6)-S(3)-O(5)	118.97(8)	O(6)-S(3)-C(9)	109.23(9)
O(5)-S(3)-C(9)	108.07(8)	O(6)-S(3)-C(27)	109.00(9)
O(5)-S(3)-C(27)	108.17(8)	C(9)-S(3)-C(27)	102.08(7)
C(1)-N(1)-C(4)	96.04(11)	C(1)-N(1)-S(1)	120.46(9)
C(4)-N(1)-S(1)	120.33(10)	C(5)-N(2)-C(10)	112.14(12)
C(5)-N(2)-C(7)	117.02(13)	C(10)-N(2)-C(7)	94.45(12)
N(1)-C(1)-C(2)	103.07(12)	N(1)-C(1)-C(6)	96.40(11)
C(2)-C(1)-C(6)	112.75(13)	N(1)-C(1)-H(1)	114.3
C(2)-C(1)-H(1)	114.3	C(6)-C(1)-H(1)	114.3
C(1)-C(2)-C(3)	102.59(13)	C(1)-C(2)-H(2A)	111.2
C(3)-C(2)-H(2A)	111.2	C(1)-C(2)-H(2B)	111.2
C(3)-C(2)-H(2B)	111.2	H(2A)-C(2)-H(2B)	109.2
C(4)-C(3)-C(2)	102.93(13)	C(4)-C(3)-H(3A)	111.2
C(2)-C(3)-H(3A)	111.2	C(4)-C(3)-H(3B)	111.2
C(2)-C(3)-H(3B)	111.2	H(3A)-C(3)-H(3B)	109.1
N(1)-C(4)-C(3)	104.08(12)	N(1)-C(4)-C(5)	99.50(11)

C(3)-C(4)-C(5)	108.92(14)	N(1)-C(4)-H(4)	114.3
C(3)-C(4)-H(4)	114.3	C(5)-C(4)-H(4)	114.3
N(2)-C(5)-C(4)	110.92(13)	N(2)-C(5)-C(6)	112.20(12)
C(4)-C(5)-C(6)	100.79(11)	N(2)-C(5)-H(5)	110.9
C(4)-C(5)-H(5)	110.9	C(6)-C(5)-H(5)	110.9
C(1)-C(6)-C(5)	103.82(11)	C(1)-C(6)-S(2)	118.23(10)
C(5)-C(6)-S(2)	111.22(10)	C(1)-C(6)-H(6)	107.7
C(5)-C(6)-H(6)	107.7	S(2)-C(6)-H(6)	107.7
N(2)-C(7)-C(8)	103.61(13)	N(2)-C(7)-C(12)	98.93(15)
C(8)-C(7)-C(12)	106.10(14)	N(2)-C(7)-H(7)	115.4
C(8)-C(7)-H(7)	115.4	C(12)-C(7)-H(7)	115.4
C(9)-C(8)-C(7)	105.46(16)	C(9)-C(8)-H(8)	127.3
C(7)-C(8)-H(8)	127.3	C(8)-C(9)-C(10)	107.21(15)
C(8)-C(9)-S(3)	127.66(14)	C(10)-C(9)-S(3)	125.07(12)
N(2)-C(10)-C(9)	102.04(12)	N(2)-C(10)-C(11)	99.60(13)
C(9)-C(10)-C(11)	105.96(15)	N(2)-C(10)-H(10)	115.7
C(9)-C(10)-H(10)	115.7	C(11)-C(10)-H(10)	115.7
C(12)-C(11)-C(10)	101.30(15)	C(12)-C(11)-H(11A)	111.5
C(10)-C(11)-H(11A)	111.5	C(12)-C(11)-H(11B)	111.5
C(10)-C(11)-H(11B)	111.5	H(11A)-C(11)-H(11B)	109.3
C(11)-C(12)-C(7)	102.51(14)	C(11)-C(12)-H(12A)	111.3
C(7)-C(12)-H(12A)	111.3	C(11)-C(12)-H(12B)	111.3
C(7)-C(12)-H(12B)	111.3	H(12A)-C(12)-H(12B)	109.2
C(18)-C(13)-C(14)	120.34(17)	C(18)-C(13)-S(1)	119.67(14)
C(14)-C(13)-S(1)	119.94(13)	C(13)-C(14)-C(15)	119.16(17)
C(13)-C(14)-H(14)	120.4	C(15)-C(14)-H(14)	120.4
C(16)-C(15)-C(14)	121.28(19)	C(16)-C(15)-H(15)	119.4
C(14)-C(15)-H(15)	119.4	C(17)-C(16)-C(15)	118.19(19)
C(17)-C(16)-C(19)	120.8(2)	C(15)-C(16)-C(19)	121.0(2)
C(16)-C(17)-C(18)	121.83(19)	C(16)-C(17)-H(17)	119.1
C(18)-C(17)-H(17)	119.1	C(13)-C(18)-C(17)	119.18(18)
C(13)-C(18)-H(18)	120.4	C(17)-C(18)-H(18)	120.4
C(16)-C(19)-H(19A)	109.5	C(16)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5	C(16)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5	H(19B)-C(19)-H(19C)	109.5
C(25)-C(20)-C(21)	120.63(16)	C(25)-C(20)-S(2)	120.38(13)
C(21)-C(20)-S(2)	118.95(12)	C(22)-C(21)-C(20)	119.03(16)
C(22)-C(21)-H(21)	120.5	C(20)-C(21)-H(21)	120.5
C(21)-C(22)-C(23)	121.59(17)	C(21)-C(22)-H(22)	119.2
C(23)-C(22)-H(22)	119.2	C(22)-C(23)-C(24)	118.09(16)
C(22)-C(23)-C(26)	121.16(18)	C(24)-C(23)-C(26)	120.75(17)
C(25)-C(24)-C(23)	121.52(16)	C(25)-C(24)-H(24)	119.2
C(23)-C(24)-H(24)	119.2	C(20)-C(25)-C(24)	119.12(16)
C(20)-C(25)-H(25)	120.4	C(24)-C(25)-H(25)	120.4
C(23)-C(26)-H(26A)	109.5	C(23)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5	C(23)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5	H(26B)-C(26)-H(26C)	109.5
C(32)-C(27)-C(28)	120.25(17)	C(32)-C(27)-S(3)	119.87(13)
C(28)-C(27)-S(3)	119.84(13)	C(29)-C(28)-C(27)	119.46(17)
C(29)-C(28)-H(28)	120.3	C(27)-C(28)-H(28)	120.3
C(28)-C(29)-C(30)	121.39(18)	C(28)-C(29)-H(29)	119.3
C(30)-C(29)-H(29)	119.3	C(29)-C(30)-C(31)	118.27(18)
C(29)-C(30)-C(33)	121.1(2)	C(31)-C(30)-C(33)	120.6(2)
C(32)-C(31)-C(30)	121.32(18)	C(32)-C(31)-H(31)	119.3
C(30)-C(31)-H(31)	119.3	C(31)-C(32)-C(27)	119.29(17)
C(31)-C(32)-H(32)	120.4	C(27)-C(32)-H(32)	120.4
C(30)-C(33)-H(33A)	109.5	C(30)-C(33)-H(33B)	109.5
H(33A)-C(33)-H(33B)	109.5	C(30)-C(33)-H(33C)	109.5
H(33A)-C(33)-H(33C)	109.5	H(33B)-C(33)-H(33C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4 - Anisotropic displacement parameters ($Å^2 \times 10^3$) for dimer **396**. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

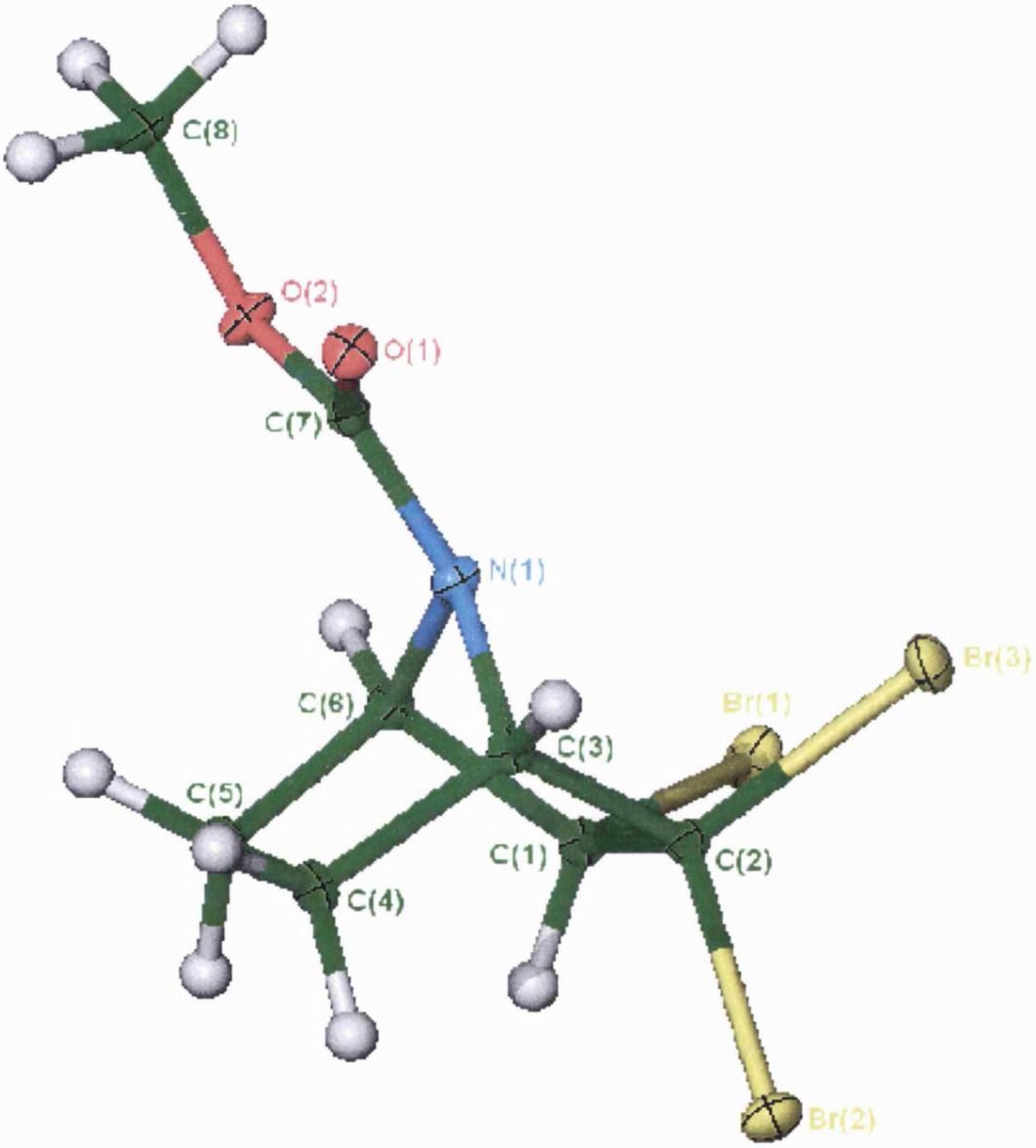
Atom	U11	U22	U33	U23	U13	U12
S(1)	45(1)	34(1)	41(1)	5(1)	13(1)	0(1)
S(2)	42(1)	33(1)	43(1)	4(1)	16(1)	2(1)
S(3)	50(1)	41(1)	38(1)	7(1)	6(1)	-1(1)
O(1)	46(1)	58(1)	50(1)	19(1)	10(1)	8(1)
O(2)	79(1)	34(1)	61(1)	-6(1)	30(1)	-9(1)
O(3)	58(1)	49(1)	51(1)	-2(1)	29(1)	1(1)
O(4)	55(1)	38(1)	58(1)	15(1)	15(1)	6(1)
O(5)	48(1)	62(1)	53(1)	5(1)	-3(1)	-2(1)
O(6)	85(1)	48(1)	57(1)	17(1)	20(1)	-6(1)
N(1)	39(1)	34(1)	33(1)	2(1)	8(1)	-2(1)
N(2)	36(1)	42(1)	39(1)	-2(1)	9(1)	8(1)
C(1)	35(1)	34(1)	37(1)	4(1)	9(1)	1(1)
C(2)	49(1)	37(1)	55(1)	11(1)	20(1)	13(1)
C(3)	71(1)	37(1)	45(1)	1(1)	21(1)	17(1)
C(4)	48(1)	33(1)	34(1)	0(1)	7(1)	0(1)
C(5)	38(1)	32(1)	33(1)	1(1)	11(1)	5(1)
C(6)	36(1)	31(1)	36(1)	1(1)	12(1)	4(1)
C(7)	47(1)	41(1)	49(1)	-7(1)	6(1)	14(1)
C(8)	49(1)	35(1)	51(1)	3(1)	7(1)	9(1)
C(9)	40(1)	40(1)	41(1)	2(1)	5(1)	7(1)
C(10)	37(1)	45(1)	41(1)	-1(1)	7(1)	2(1)
C(11)	39(1)	82(1)	62(1)	-1(1)	13(1)	12(1)
C(12)	53(1)	79(1)	62(1)	-11(1)	11(1)	29(1)
C(13)	44(1)	41(1)	39(1)	3(1)	13(1)	-4(1)
C(14)	52(1)	59(1)	43(1)	-3(1)	11(1)	-2(1)
C(15)	75(1)	76(1)	46(1)	-4(1)	24(1)	6(1)
C(16)	65(1)	84(2)	63(1)	5(1)	32(1)	6(1)
C(17)	45(1)	117(2)	66(1)	-5(1)	18(1)	-8(1)
C(18)	47(1)	89(2)	47(1)	-10(1)	12(1)	-12(1)
C(19)	90(2)	157(3)	97(2)	6(2)	59(2)	18(2)
C(20)	41(1)	32(1)	47(1)	3(1)	18(1)	-1(1)
C(21)	43(1)	40(1)	61(1)	-2(1)	21(1)	3(1)
C(22)	53(1)	48(1)	57(1)	-9(1)	24(1)	-2(1)
C(23)	50(1)	45(1)	50(1)	5(1)	18(1)	-7(1)
C(24)	40(1)	57(1)	61(1)	1(1)	16(1)	5(1)
C(25)	46(1)	47(1)	56(1)	-4(1)	21(1)	6(1)
C(26)	58(1)	69(1)	59(1)	-3(1)	12(1)	-10(1)
C(27)	51(1)	40(1)	37(1)	1(1)	15(1)	-6(1)
C(28)	53(1)	46(1)	55(1)	-1(1)	18(1)	-10(1)
C(29)	72(1)	40(1)	69(1)	-5(1)	29(1)	-8(1)
C(30)	73(1)	54(1)	61(1)	-2(1)	36(1)	6(1)
C(31)	53(1)	64(1)	58(1)	-1(1)	30(1)	-1(1)
C(32)	53(1)	51(1)	49(1)	-2(1)	22(1)	-12(1)
C(33)	98(2)	70(2)	124(2)	-9(2)	52(2)	23(1)

Table 5 - Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for dimer **396**

Atom	x	y	z	U(eq)
H(1)	173	3751	579	43
H(2A)	-108	4661	1300	56
H(2B)	-25	6087	961	56
H(3A)	576	6992	1638	61
H(3B)	522	5479	1962	61
H(4)	1283	5587	1711	48
H(5)	942	3090	2037	42
H(6)	706	1779	1070	41
H(7)	1265	21	1569	58
H(8)	1389	-424	2495	57
H(10)	1886	4019	2322	51
H(11A)	2399	2677	1937	75
H(11B)	2518	1738	2459	75
H(12A)	2165	-512	2037	80
H(12B)	2046	427	1516	80
H(14)	836	4930	-291	63
H(15)	1412	4340	-645	78
H(17)	2426	5822	618	92
H(18)	1860	6474	974	74
H(19A)	2264	3724	-498	161
H(19B)	2656	4475	-22	161
H(19C)	2385	5582	-487	161
H(21)	130	-805	687	57
H(22)	-478	-1697	-24	61
H(24)	-1405	1106	337	64
H(25)	-802	2035	1046	58
H(26A)	-1633	-1550	-295	96
H(26B)	-1271	-1644	-588	96
H(26C)	-1552	-29	-592	96
H(28)	2026	5601	3393	62
H(29)	1561	7869	3350	71
H(31)	393	5083	2970	66
H(32)	853	2790	3030	60
H(33A)	794	9015	3349	141
H(33B)	334	7931	3162	141
H(33C)	544	8669	2768	141

Appendix B

Crystal structure and data for tribromide **404**



2,2,*exo*-3-Tribromo-7-aza-bicyclo[2.2.1]heptane-7-carboxylic acid methyl ester

Table 1 - Crystal data and structure refinement for **404**

Identification code	tribromide **404**
Empirical formula	C8 H10 Br3 N O2
Formula weight	391.90
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 7.2870(1)Å α = 90°
	b = 18.5090(3)Å β = 93.514(1)°
	c = 8.2610(1)Å γ = 90°
Volume	1112.11(3) Å^3
Z	4
Density (calculated)	2.341 Mg/m^3
Absorption coefficient	10.856 mm^{-1}
F(000)	744
Crystal size	0.40 x 0.25 x 0.13 mm
Theta range for data collection	3.56 to 32.06 °.
Index ranges	-10<=h<=10; -27<=k<=27; -12<=l<=12
Reflections collected	23266
Independent reflections	3862 [R(int) = 0.0965]
Reflections observed (>2σ)	3358
Data Completeness	0.997
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.39 and 0.14
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3862 / 0 / 129
Goodness-of-fit on F^2	1.069
Final R indices [I>2σ(I)]	R_1 = 0.0523 wR_2 = 0.1330
R indices (all data)	R_1 = 0.0590 wR_2 = 0.1386
Largest diff. peak and hole	2.282 and -2.051 e.Å^{-3}

Table 2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **404**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Br(1)	8668(1)	6031(1)	6885(1)	29(1)
Br(2)	3340(1)	5250(1)	7091(1)	26(1)
Br(3)	5558(1)	6236(1)	9602(1)	27(1)
O(1)	3369(4)	8348(1)	7629(3)	25(1)
O(2)	5930(4)	8457(1)	6211(3)	26(1)
N(1)	4963(4)	7355(1)	6816(3)	19(1)
C(1)	6166(4)	6237(2)	6097(4)	20(1)
C(2)	4664(4)	6162(2)	7347(4)	19(1)
C(3)	3451(4)	6833(2)	6915(4)	19(1)
C(4)	2617(5)	6798(2)	5145(4)	24(1)
C(5)	4289(5)	6977(2)	4133(4)	26(1)
C(6)	5867(4)	7015(2)	5454(4)	20(1)
C(7)	4630(4)	8082(2)	6928(4)	20(1)
C(8)	5816(6)	9233(2)	6381(5)	31(1)

Table 3 - Bond lengths [Å] and angles [°] for **404**

Br(1)-C(1)	1.936(3)	Br(2)-C(2)	1.950(3)
Br(3)-C(2)	1.940(3)	O(1)-C(7)	1.219(4)
O(2)-C(7)	1.341(4)	O(2)-C(8)	1.447(4)
N(1)-C(7)	1.371(4)	N(1)-C(3)	1.471(4)
N(1)-C(6)	1.479(4)	C(1)-C(6)	1.544(4)
C(1)-C(2)	1.557(5)	C(2)-C(3)	1.553(4)

C(3)-C(4)	1.550(4)	C(4)-C(5)	1.555(5)
C(5)-C(6)	1.538(5)		
C(7)-O(2)-C(8)	115.1(3)	C(7)-N(1)-C(3)	120.3(3)
C(7)-N(1)-C(6)	123.9(3)	C(3)-N(1)-C(6)	97.6(2)
C(6)-C(1)-C(2)	102.8(2)	C(6)-C(1)-Br(1)	114.2(2)
C(2)-C(1)-Br(1)	116.4(2)	C(3)-C(2)-C(1)	100.9(2)
C(3)-C(2)-Br(3)	108.5(2)	C(1)-C(2)-Br(3)	115.0(2)
C(3)-C(2)-Br(2)	113.3(2)	C(1)-C(2)-Br(2)	111.6(2)
Br(3)-C(2)-Br(2)	107.45(14)	N(1)-C(3)-C(4)	103.1(3)
N(1)-C(3)-C(2)	96.9(2)	C(4)-C(3)-C(2)	111.6(3)
C(3)-C(4)-C(5)	102.9(3)	C(6)-C(5)-C(4)	101.8(3)
N(1)-C(6)-C(5)	102.1(3)	N(1)-C(6)-C(1)	101.3(2)
C(5)-C(6)-C(1)	106.6(3)	O(1)-C(7)-O(2)	125.0(3)
O(1)-C(7)-N(1)	124.7(3)	O(2)-C(7)-N(1)	110.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 4 - Anisotropic displacement parameters ($Å^2 \times 10^3$) for **404**. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

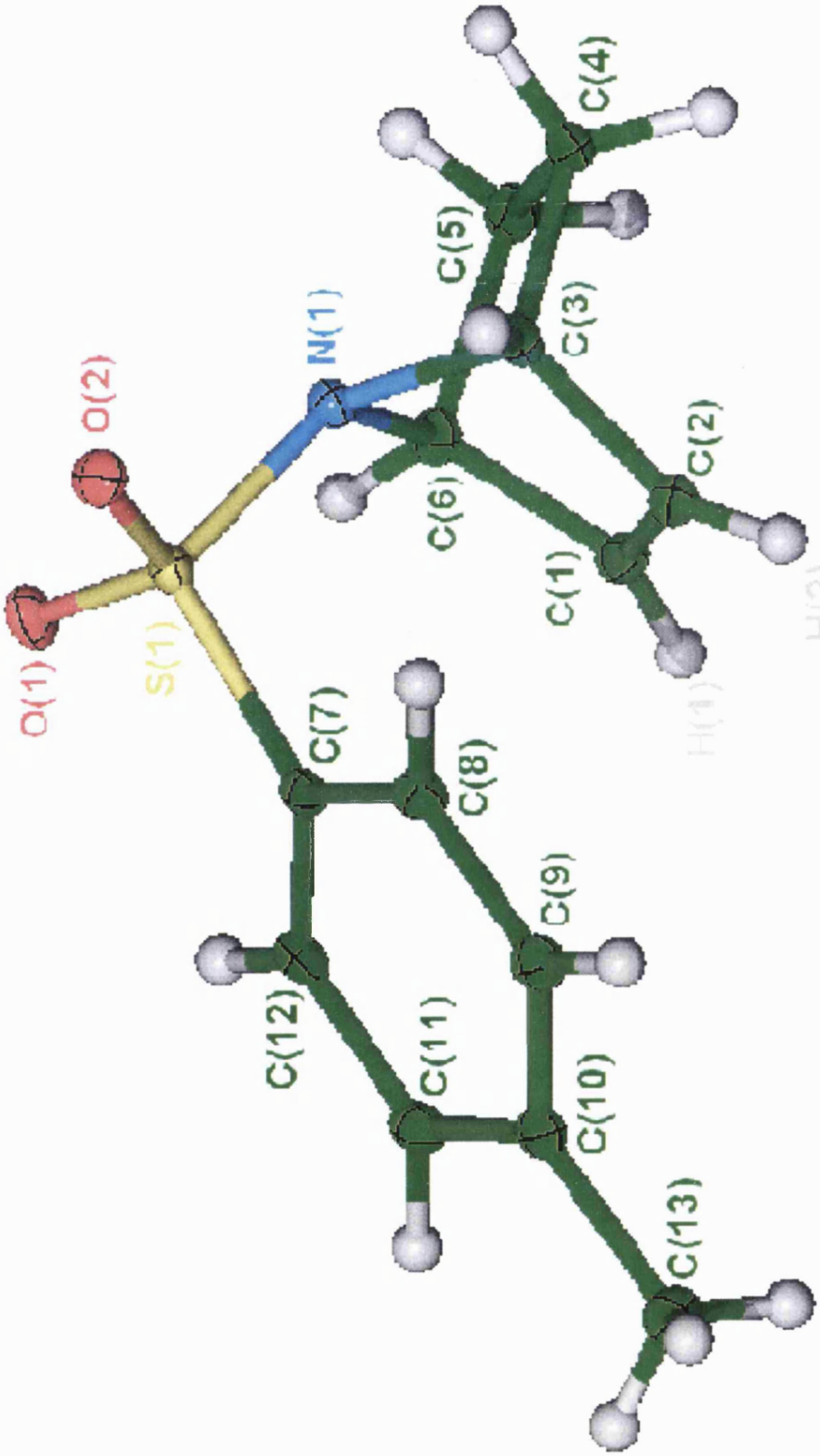
Atom	U11	U22	U33	U23	U13	U12
Br(1)	18(1)	30(1)	41(1)	8(1)	4(1)	4(1)
Br(2)	24(1)	21(1)	35(1)	-1(1)	6(1)	-5(1)
Br(3)	29(1)	35(1)	18(1)	4(1)	0(1)	-2(1)
O(1)	25(1)	26(1)	26(1)	-1(1)	8(1)	4(1)
O(2)	25(1)	17(1)	35(1)	3(1)	8(1)	0(1)
N(1)	19(1)	18(1)	22(1)	0(1)	7(1)	-1(1)
C(1)	19(1)	22(1)	20(1)	0(1)	3(1)	1(1)
C(2)	20(1)	18(1)	19(1)	0(1)	2(1)	-1(1)
C(3)	17(1)	20(1)	21(1)	-1(1)	4(1)	-1(1)
C(4)	22(1)	30(2)	21(1)	1(1)	-1(1)	2(1)
C(5)	24(2)	32(2)	20(1)	2(1)	3(1)	2(1)
C(6)	19(1)	21(1)	20(1)	1(1)	6(1)	0(1)
C(7)	19(1)	22(1)	18(1)	2(1)	2(1)	0(1)
C(8)	38(2)	15(1)	42(2)	1(1)	9(2)	0(1)

Table 5 - Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **404**

Atom	x	y	z	U(eq)
H(1)	5843	5898	5181	24
H(3)	2549	6956	7737	23
H(4A)	1623	7158	4956	29
H(4B)	2125	6311	4881	29
H(5A)	4502	6593	3333	31
H(5B)	4121	7445	3560	31
H(6)	7002	7265	5126	24
H(8A)	4676	9407	5823	47
H(8B)	6872	9459	5901	47
H(8C)	5825	9359	7534	47

Appendix C

Crystal Structure and data of alkene **405**



7-(Toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene

Table 1 - Crystal data and structure refinement for **405**

Identification code	Alkene **405**
Empirical formula	C26 H30 N2 O4 S2
Formula weight	498.64
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 7.43400(10)Å α = 90°
	b = 8.8930(2)Å β = 93.1230(10)°
	c = 18.4010(5)Å γ = 90°
Volume	1214.69(5) $Å^3$
Z	2
Density (calculated)	1.363 Mg/m^3
Absorption coefficient	0.255 mm^{-1}
F(000)	528
Crystal size	0.25 x 0.10 x 0.10 mm
Theta range for data collection	3.70 to 27.51 °.
Index ranges	-9<=h<=9; -11<=k<=11; -23<=l<=23
Reflections collected	16841
Independent reflections	2770 [R(int) = 0.0519]
Reflections observed (>2σ)	2159
Data Completeness	0.993
Max. and min. transmission	0.9749 and 0.9389
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2770 / 3 / 167
Goodness-of-fit on F^2	1.024
Final R indices [I>2σ(I)]	R_1 = 0.0391 wR_2 = 0.0945
R indices (all data)	R_1 = 0.0582 wR_2 = 0.1052
Largest diff. peak and hole	0.253 and -0.452 $eÅ^{-3}$

Table 2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **405**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
S(1)	8284(1)	-310(1)	8422(1)	25(1)
O(1)	9050(2)	852(1)	8883(1)	36(1)
O(2)	9090(2)	-684(2)	7756(1)	33(1)
N(1)	6243(2)	258(2)	8177(1)	24(1)
C(1)	4065(2)	-623(2)	8953(1)	30(1)
C(2)	4049(2)	-1561(2)	8397(1)	30(1)
C(3)	4934(2)	-760(2)	7781(1)	27(1)
C(4)	3559(2)	447(2)	7507(1)	33(1)
C(5)	3578(2)	1556(2)	8152(1)	34(1)
C(6)	4955(2)	818(2)	8709(1)	29(1)
C(7)	8165(2)	-1974(2)	8937(1)	24(1)
C(8)	7793(2)	-3328(2)	8578(1)	27(1)
C(9)	7557(2)	-4618(2)	8982(1)	29(1)
C(10)	7695(2)	-4594(2)	9740(1)	29(1)
C(11)	8107(2)	-3233(2)	10083(1)	32(1)
C(12)	8333(2)	-1925(2)	9692(1)	28(1)
C(13)	7396(3)	-6000(3)	10170(1)	42(1)

Table 3 - Bond lengths [Å] and angles [°] for **405**

S(1)-O(2)	1.4334(13)	S(1)-O(1)	1.4342(13)
S(1)-N(1)	1.6391(14)	S(1)-C(7)	1.7617(17)
N(1)-C(3)	1.490(2)	N(1)-C(6)	1.491(2)
C(1)-C(2)	1.319(3)	C(1)-C(6)	1.521(2)
C(2)-C(3)	1.519(2)	C(3)-C(4)	1.548(2)
C(4)-C(5)	1.542(3)	C(5)-C(6)	1.554(3)

C(7)-C(12)	1.389(2)	C(7)-C(8)	1.394(2)
C(8)-C(9)	1.383(2)	C(9)-C(10)	1.393(2)
C(10)-C(11)	1.391(3)	C(10)-C(13)	1.503(3)
C(11)-C(12)	1.383(3)		
O(2)-S(1)-O(1)	120.11(8)	O(2)-S(1)-N(1)	105.04(7)
O(1)-S(1)-N(1)	105.83(7)	O(2)-S(1)-C(7)	107.51(8)
O(1)-S(1)-C(7)	108.47(8)	N(1)-S(1)-C(7)	109.54(7)
C(3)-N(1)-C(6)	95.59(13)	C(3)-N(1)-S(1)	121.19(11)
C(6)-N(1)-S(1)	122.67(11)	C(2)-C(1)-C(6)	106.80(16)
C(1)-C(2)-C(3)	107.22(16)	N(1)-C(3)-C(2)	102.60(13)
N(1)-C(3)-C(4)	98.07(14)	C(2)-C(3)-C(4)	105.30(14)
C(5)-C(4)-C(3)	102.37(14)	C(4)-C(5)-C(6)	102.43(14)
N(1)-C(6)-C(1)	102.61(14)	N(1)-C(6)-C(5)	97.57(13)
C(1)-C(6)-C(5)	105.65(15)	C(12)-C(7)-C(8)	120.39(16)
C(12)-C(7)-S(1)	120.48(13)	C(8)-C(7)-S(1)	119.02(13)
C(9)-C(8)-C(7)	119.36(16)	C(8)-C(9)-C(10)	121.31(17)
C(11)-C(10)-C(9)	118.08(16)	C(11)-C(10)-C(13)	121.32(18)
C(9)-C(10)-C(13)	120.60(19)	C(12)-C(11)-C(10)	121.73(16)
C(11)-C(12)-C(7)	119.12(17)		

Symmetry transformations used to generate equivalent atoms:

Table 4 - Anisotropic displacement parameters ($Å^2 \times 10^3$) for **405**. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

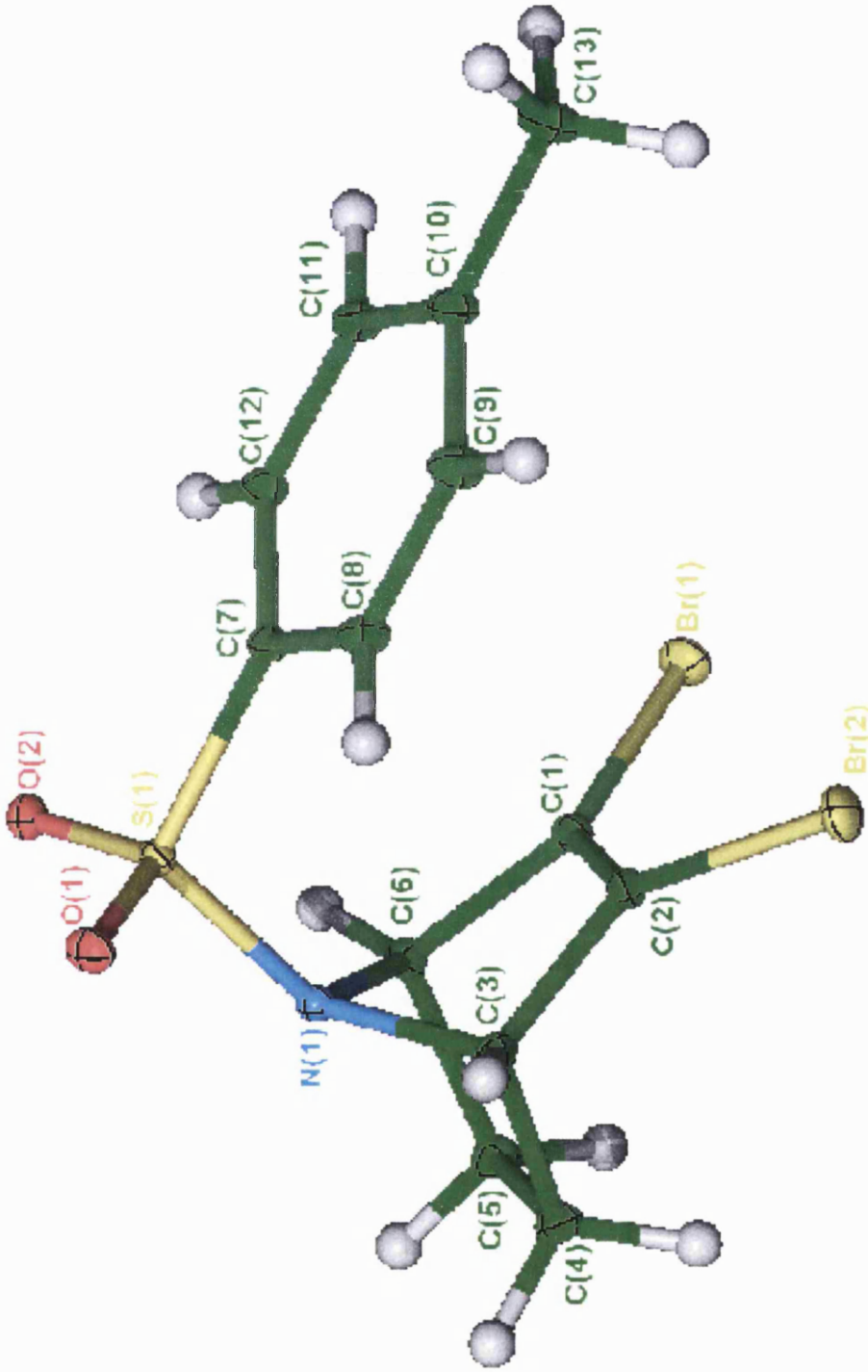
Atom	U11	U22	U33	U23	U13	U12
S(1)	18(1)	28(1)	29(1)	2(1)	-1(1)	-1(1)
O(1)	29(1)	31(1)	46(1)	-3(1)	-9(1)	-7(1)
O(2)	24(1)	44(1)	32(1)	6(1)	8(1)	2(1)
N(1)	18(1)	25(1)	28(1)	2(1)	0(1)	0(1)
C(1)	27(1)	34(1)	30(1)	7(1)	5(1)	1(1)
C(2)	24(1)	28(1)	37(1)	7(1)	-1(1)	-4(1)
C(3)	22(1)	31(1)	27(1)	0(1)	-2(1)	-3(1)
C(4)	20(1)	44(1)	34(1)	11(1)	-1(1)	-1(1)
C(5)	23(1)	32(1)	49(1)	9(1)	5(1)	4(1)
C(6)	26(1)	27(1)	33(1)	-2(1)	4(1)	0(1)
C(7)	18(1)	28(1)	25(1)	0(1)	1(1)	4(1)
C(8)	27(1)	31(1)	22(1)	-3(1)	1(1)	3(1)
C(9)	26(1)	29(1)	31(1)	-1(1)	2(1)	2(1)
C(10)	18(1)	38(1)	32(1)	7(1)	3(1)	3(1)
C(11)	27(1)	46(1)	22(1)	3(1)	1(1)	3(1)
C(12)	23(1)	35(1)	25(1)	-5(1)	-3(1)	3(1)
C(13)	31(1)	49(1)	46(1)	19(1)	2(1)	-3(1)

Table 5 - Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **405**

Atom	x	y	z	U(eq)
H(1)	3646	-697	9436	36
H(2)	3606	-2569	8333	36
H(3)	5572	-1354	7444	32
H(4A)	2364	56	7416	39
H(4B)	3922	975	7084	39
H(5A)	2426	1625	8361	41
H(5B)	3983	2545	8029	41
H(6)	5594	1420	9070	34
H(8)	7703	-3364	8062	32
H(9)	7278	-5543	8730	34
H(11)	8247	-3228	10605	38
H(12)	8595	-1001	9947	33
H(13A)	8080(30)	-5980(30)	10569(10)	64(8)
H(13B)	6300(30)	-6060(30)	10277(15)	80(9)
H(13C)	7750(40)	-6820(30)	9949(15)	89(11)

Appendix D

Crystal structure and data of dibromide **409**



2,3-Dibromo-7-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-2-ene

Table 1 - Crystal data and structure refinement for dibromide **409**

Identification code	dibromide **409**
Empirical formula	$C_{13}H_{13}Br_2NO_2S$
Formula weight	407.12
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 7.70000(10)Å α = 90°
	b = 13.5330(2)Å β = 97.3260(10)°
	c = 13.9150(2)Å γ = 90°
Volume	1438.16(4) Å^3
Z	4
Density (calculated)	1.880 Mg/m^3
Absorption coefficient	5.778 mm^{-1}
F(000)	800
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	4.49 to 27.48°
Index ranges	-9<=h<=9; -16<=k<=17; -18<=l<=18
Reflections collected	20658
Independent reflections	3271 [R(int) = 0.0295]
Reflections observed (>2σ)	3098
Data Completeness	0.994
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.20 and 0.17
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3271 / 0 / 173
Goodness-of-fit on F^2	1.077
Final R indices [I>2σ(I)]	R_1 = 0.0211 wR_2 = 0.0511
R indices (all data)	R_1 = 0.0229 wR_2 = 0.0520
Largest diff. peak and hole	0.507 and -0.444 eÅ^{-3}

Table 2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for dibromide **409**. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

Atom	x	y	z	U(eq)
Br(1)	6712(1)	3513(1)	2213(1)	28(1)
Br(2)	6261(1)	2661(1)	-329(1)	29(1)
S(1)	10475(1)	760(1)	1788(1)	17(1)
O(1)	10947(2)	-35(1)	1188(1)	24(1)
O(2)	11132(2)	781(1)	2801(1)	23(1)
N(1)	8329(2)	682(1)	1755(1)	17(1)
C(1)	7077(2)	2262(1)	1718(1)	19(1)
C(2)	6920(2)	1950(1)	806(1)	19(1)
C(3)	7127(2)	828(1)	837(1)	18(1)
C(4)	5418(2)	432(1)	1189(1)	23(1)
C(5)	5598(2)	800(1)	2257(1)	23(1)
C(6)	7381(2)	1351(1)	2357(1)	19(1)
C(7)	11045(2)	1876(1)	1265(1)	18(1)
C(8)	10946(2)	1946(1)	263(1)	22(1)
C(9)	11339(3)	2842(2)	-142(1)	26(1)
C(10)	11850(2)	3663(1)	436(2)	25(1)
C(11)	11931(3)	3569(1)	1436(1)	24(1)
C(12)	11531(2)	2685(1)	1858(1)	22(1)
C(13)	12331(3)	4624(2)	-9(2)	36(1)

Table 3 - Bond lengths [Å] and angles [°] for dibromide **409**

Br(1)-C(1)	1.8624(17)	Br(2)-C(2)	1.8632(18)
S(1)-O(1)	1.4366(14)	S(1)-O(2)	1.4363(13)
S(1)-N(1)	1.6506(15)	S(1)-C(7)	1.7568(18)
N(1)-C(6)	1.486(2)	N(1)-C(3)	1.492(2)
C(1)-C(2)	1.329(3)	C(1)-C(6)	1.521(2)
C(2)-C(3)	1.527(2)	C(3)-C(4)	1.556(2)
C(4)-C(5)	1.556(3)	C(5)-C(6)	1.553(2)
C(7)-C(8)	1.391(2)	C(7)-C(12)	1.392(2)
C(8)-C(9)	1.385(3)	C(9)-C(10)	1.399(3)
C(10)-C(11)	1.391(3)	C(10)-C(13)	1.507(3)
C(11)-C(12)	1.384(3)		
O(1)-S(1)-O(2)	120.12(8)	O(1)-S(1)-N(1)	105.22(8)
O(2)-S(1)-N(1)	104.75(8)	O(1)-S(1)-C(7)	107.99(8)
O(2)-S(1)-C(7)	108.29(8)	N(1)-S(1)-C(7)	110.20(8)
C(6)-N(1)-C(3)	96.07(12)	C(6)-N(1)-S(1)	120.49(11)
C(3)-N(1)-S(1)	121.66(12)	C(2)-C(1)-C(6)	106.78(15)
C(2)-C(1)-Br(1)	130.03(14)	C(6)-C(1)-Br(1)	122.69(13)
C(1)-C(2)-C(3)	107.01(15)	C(1)-C(2)-Br(2)	128.78(14)
C(3)-C(2)-Br(2)	123.69(13)	N(1)-C(3)-C(2)	101.97(13)
N(1)-C(3)-C(4)	98.18(14)	C(2)-C(3)-C(4)	105.18(14)
C(3)-C(4)-C(5)	102.38(14)	C(6)-C(5)-C(4)	102.07(14)
N(1)-C(6)-C(1)	102.42(14)	N(1)-C(6)-C(5)	98.57(13)
C(1)-C(6)-C(5)	105.57(14)	C(8)-C(7)-C(12)	121.09(17)
C(8)-C(7)-S(1)	119.30(14)	C(12)-C(7)-S(1)	119.57(14)
C(9)-C(8)-C(7)	118.70(17)	C(8)-C(9)-C(10)	121.42(18)
C(11)-C(10)-C(9)	118.43(17)	C(11)-C(10)-C(13)	120.56(18)
C(9)-C(10)-C(13)	121.01(19)	C(12)-C(11)-C(10)	121.26(17)
C(11)-C(12)-C(7)	119.09(17)		

Symmetry transformations used to generate equivalent atoms:

Table 4 - Anisotropic displacement parameters ($Å^2 \times 10^3$) for dibromide **409**. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

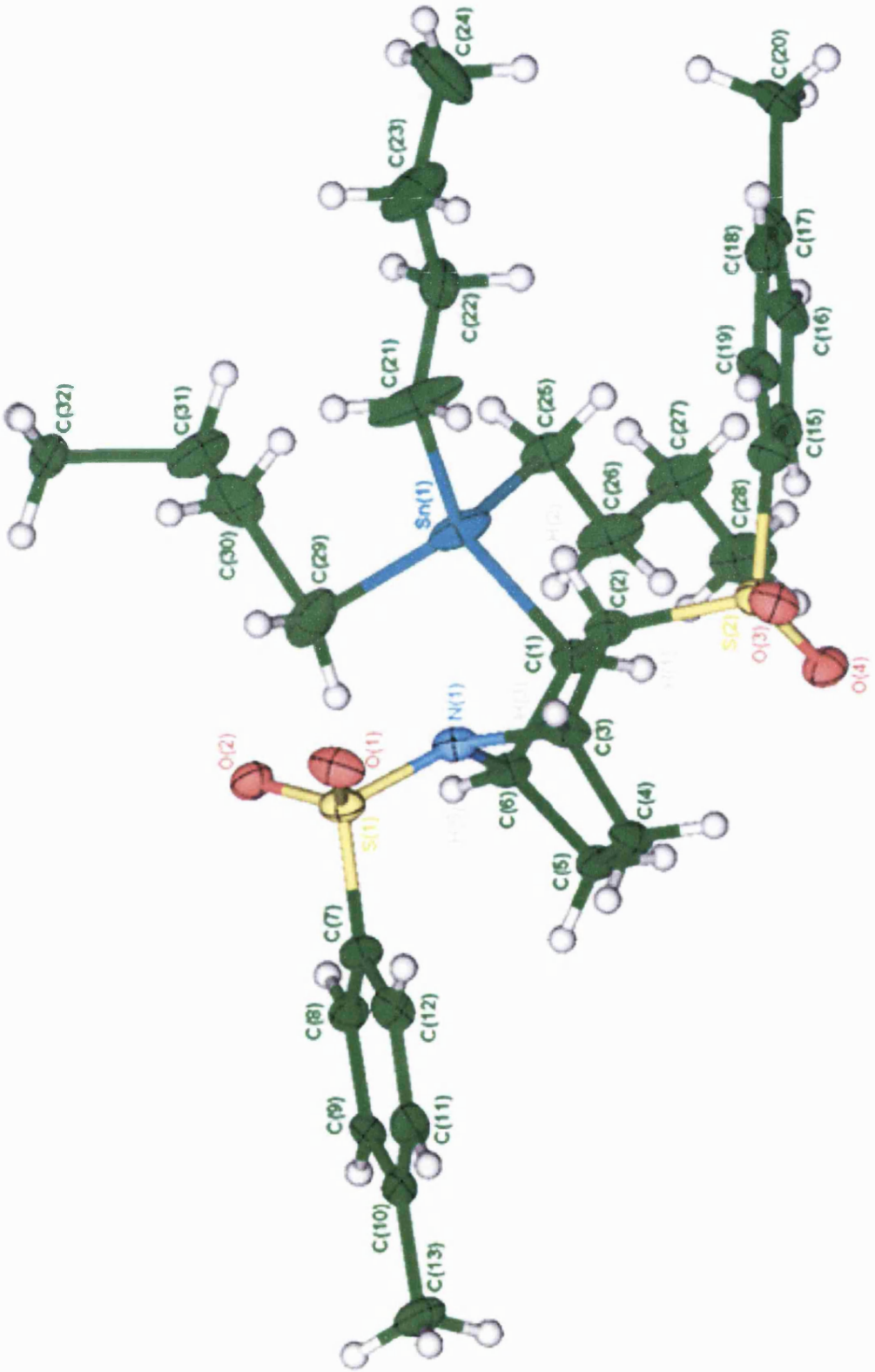
Atom	U11	U22	U33	U23	U13	U12
Br(1)	30(1)	18(1)	36(1)	-7(1)	6(1)	3(1)
Br(2)	32(1)	30(1)	24(1)	8(1)	1(1)	5(1)
S(1)	16(1)	15(1)	20(1)	1(1)	3(1)	1(1)
O(1)	24(1)	18(1)	32(1)	-3(1)	9(1)	2(1)
O(2)	23(1)	24(1)	21(1)	4(1)	-2(1)	0(1)
N(1)	17(1)	16(1)	17(1)	0(1)	3(1)	0(1)
C(1)	18(1)	15(1)	24(1)	-1(1)	5(1)	1(1)
C(2)	18(1)	19(1)	22(1)	3(1)	2(1)	1(1)
C(3)	18(1)	19(1)	18(1)	-2(1)	0(1)	0(1)
C(4)	19(1)	22(1)	28(1)	-3(1)	3(1)	-3(1)
C(5)	19(1)	24(1)	26(1)	1(1)	6(1)	-2(1)
C(6)	19(1)	19(1)	19(1)	-2(1)	5(1)	2(1)
C(7)	17(1)	16(1)	21(1)	1(1)	4(1)	-2(1)
C(8)	25(1)	21(1)	22(1)	-4(1)	6(1)	-5(1)
C(9)	32(1)	27(1)	20(1)	1(1)	7(1)	-7(1)
C(10)	24(1)	21(1)	30(1)	2(1)	6(1)	-5(1)
C(11)	26(1)	20(1)	26(1)	-3(1)	2(1)	-4(1)
C(12)	24(1)	22(1)	20(1)	-2(1)	1(1)	-3(1)
C(13)	47(1)	25(1)	36(1)	4(1)	8(1)	-11(1)

Table 5 - Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for dibromide **409**

Atom	x	y	z	U(eq)
H(3)	7483	509	244	22
H(4A)	5360	-298	1155	27
H(4B)	4366	714	802	27
H(5A)	4630	1252	2364	27
H(5B)	5625	241	2717	27
H(6)	7952	1469	3034	22
H(8)	10616	1391	-137	27
H(9)	11259	2899	-826	31
H(11)	12268	4122	1838	29
H(12)	11587	2631	2542	27
H(13A)	11360	4843	-486	54
H(13B)	13380	4528	-330	54
H(13C)	12565	5125	499	54

Appendix E

Crystal structure and data of stannane **412**



2,7-Bis-(toluene-4-sulphonyl)-3-tributylstannanyl-7-aza-bicyclo[2.2.1]heptane

Table 1 - Crystal data and structure refinement for **412**

Identification code	stannane **412**
Empirical formula	C32 H47 N O4 S2 Sn
Formula weight	692.52
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 11.72100(10)Å α = 90°
	b = 27.0760(2)Å β = 92.795(1)°
	c = 21.3380(3)Å γ = 90°
Volume	6763.72(12) Å^3
Z	8
Density (calculated)	1.360 Mg/m^3
Absorption coefficient	0.913 mm^{-1}
F(000)	2880
Crystal size	0.38 x 0.25 x 0.13 mm
Theta range for data collection	3.56 to 27.53 .
Index ranges	-15<=h<=15; -35<=k<=35; -27<=l<=27
Reflections collected	109846
Independent reflections	15505 [R(int) = 0.0706]
Reflections observed (>2σ)	9394
Data Completeness	0.995
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.84 and 0.76
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15505 / 0 / 779
Goodness-of-fit on F^2	1.168
Final R indices [I>2σ(I)]	R_1 = 0.0969 wR_2 = 0.2049
R indices (all data)	R_1 = 0.1569 wR_2 = 0.2308
Largest diff. peak and hole	3.847 and -2.874 eÅ^{-3}

Notes: 2 molecules in asymmetric unit, related by pseudo non–crystallographic inversion centre.

The 3 outermost carbons in one butyl group on each tin centre are disordered in a 1:1 ratio.

Table 2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for stannane **412**. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

Atom	x	y	z	U(eq)
Sn(1)	4796(1)	7468(1)	2705(1)	67(1)
Sn(2)	5138(1)	4880(1)	2444(1)	100(1)
S(1)	3986(2)	8854(1)	3922(1)	47(1)
S(2)	3438(2)	8624(1)	1387(1)	47(1)
S(101)	6057(2)	3552(1)	1145(1)	55(1)
S(102)	6597(2)	3685(1)	3676(1)	55(1)
O(1)	2797(5)	8980(2)	3934(3)	64(2)
O(2)	4456(5)	8468(2)	4314(3)	55(2)
O(3)	2449(5)	8948(2)	1363(3)	57(2)
O(4)	4474(5)	8790(2)	1119(3)	57(2)
O(101)	5633(7)	3960(2)	778(4)	81(2)
O(102)	7239(5)	3414(3)	1133(3)	68(2)
O(103)	5582(5)	3498(3)	3946(3)	70(2)
O(104)	7599(5)	3372(2)	3676(3)	60(2)
N(1)	4174(5)	8678(2)	3199(3)	45(2)
N(101)	5841(5)	3696(2)	1857(3)	45(2)
C(1)	4885(6)	8237(3)	2376(4)	43(2)
C(2)	3702(6)	8474(3)	2196(4)	46(2)
C(3)	3618(6)	8925(3)	2636(4)	47(2)
C(4)	4468(7)	9326(3)	2477(4)	47(2)

C(5)	5646(6)	9082(3)	2644(4)	44(2)
C(6)	5307(6)	8580(3)	2928(4)	43(2)
C(7)	4793(7)	9391(3)	4090(4)	45(2)
C(8)	5954(7)	9351(3)	4217(4)	46(2)
C(9)	6596(8)	9776(3)	4325(4)	52(2)
C(10)	6086(10)	10238(3)	4305(4)	62(3)
C(11)	4925(10)	10266(3)	4186(4)	61(3)
C(12)	4274(8)	9852(3)	4066(4)	52(2)
C(13)	6791(12)	10700(4)	4424(6)	97(4)
C(14)	3033(7)	8053(3)	1051(4)	47(2)
C(15)	3844(7)	7719(3)	859(4)	46(2)
C(16)	3497(8)	7266(4)	634(4)	57(2)
C(17)	2352(9)	7137(3)	582(4)	54(2)
C(18)	1552(8)	7477(4)	748(4)	56(2)
C(19)	1881(7)	7934(4)	989(4)	54(2)
C(20)	1967(11)	6640(4)	339(5)	83(4)
C(21)	3029(9)	7255(4)	2762(9)	130(7)
C(22)	2704(8)	6806(5)	2417(5)	76(3)
C(23)	1443(10)	6666(5)	2424(8)	111(5)
C(24)	1120(14)	6221(8)	2050(6)	173(10)
C(25)	5620(8)	7001(3)	2046(5)	59(2)
C(26)	6759(8)	7195(3)	1834(6)	76(3)
C(27)	7268(9)	6886(4)	1333(6)	82(4)
C(28)	8394(10)	7069(4)	1108(7)	93(4)
C(29)	5716(12)	7420(4)	3602(6)	95(4)
C(30)	5210(20)	6867(8)	3784(12)	84(7)
C(31)	5510(20)	6498(8)	3866(14)	86(8)
C(32)	5390(20)	6313(9)	4653(11)	69(6)
C(33)	6329(18)	6932(6)	3843(9)	55(5)
C(34)	5650(30)	6816(10)	4412(11)	110(12)
C(35)	4810(20)	6490(20)	4416(18)	150(20)
C(101)	6301(7)	3867(3)	2881(4)	49(2)
C(102)	5101(7)	4101(3)	2697(5)	62(3)
C(103)	4701(7)	3783(3)	2120(5)	50(2)
C(104)	4372(6)	3260(3)	2362(4)	45(2)
C(105)	5537(7)	3020(3)	2551(5)	50(2)
C(106)	6396(7)	3433(3)	2415(4)	48(2)
C(107)	5236(7)	3030(3)	910(4)	46(2)
C(108)	5727(9)	2568(3)	928(5)	59(2)
C(109)	5075(11)	2161(4)	738(5)	72(3)
C(110)	3967(12)	2213(5)	522(5)	81(4)
C(111)	3481(10)	2676(6)	511(5)	84(4)
C(112)	4105(8)	3095(4)	698(4)	61(3)
C(113)	3267(15)	1768(6)	301(7)	139(7)
C(114)	6981(7)	4244(3)	4051(4)	53(2)
C(115)	8126(8)	4379(3)	4105(4)	57(2)
C(116)	8429(9)	4827(4)	4368(4)	63(3)
C(117)	7616(10)	5148(4)	4588(5)	69(3)
C(118)	6481(10)	4999(4)	4543(5)	81(4)
C(119)	6157(9)	4552(4)	4278(5)	70(3)
C(120)	7954(12)	5643(4)	4867(6)	94(4)
C(121)	4340(9)	5330(4)	3130(8)	106(5)
C(122)	3115(9)	5191(4)	3228(6)	79(3)
C(123)	2560(9)	5512(4)	3719(6)	78(3)
C(124)	1327(10)	5370(5)	3804(7)	98(4)
C(125)	6886(11)	5101(4)	2403(12)	177(10)
C(126)	7172(10)	5577(5)	2756(7)	105(5)
C(127)	8374(11)	5728(6)	2754(9)	133(7)
C(128)	8580(16)	6219(9)	3082(7)	200(12)
C(129)	4131(12)	4959(5)	1554(8)	117(5)
C(130)	3585(16)	5457(6)	1321(10)	51(5)
C(131)	4430(20)	5873(8)	1269(17)	89(9)
C(132)	5110(20)	5835(12)	751(14)	99(9)
C(133)	4640(40)	5509(12)	1469(13)	134(14)
C(134)	4230(50)	5593(11)	856(14)	148(18)
C(135)	4640(40)	5242(14)	399(12)	200(20)

Table 3 - Bond lengths [Å] and angles [°] for stannane **412**

Sn(1)-C(25)	2.155(9)	Sn(1)-C(29)	2.155(14)
Sn(1)-C(21)	2.159(10)	Sn(1)-C(1)	2.200(8)
Sn(2)-C(125)	2.141(12)	Sn(2)-C(121)	2.152(12)
Sn(2)-C(102)	2.180(9)	Sn(2)-C(129)	2.197(16)
S(1)-O(2)	1.432(6)	S(1)-O(1)	1.436(6)
S(1)-N(1)	1.640(7)	S(1)-C(7)	1.763(8)
S(2)-O(4)	1.440(6)	S(2)-O(3)	1.453(6)
S(2)-C(14)	1.759(9)	S(2)-C(2)	1.786(9)
S(101)-O(101)	1.429(7)	S(101)-O(102)	1.436(6)
S(101)-N(101)	1.601(7)	S(101)-C(107)	1.768(8)
S(102)-O(103)	1.439(6)	S(102)-O(104)	1.449(6)
S(102)-C(114)	1.762(8)	S(102)-C(101)	1.784(10)
N(1)-C(6)	1.499(9)	N(1)-C(3)	1.497(11)
N(101)-C(103)	1.494(10)	N(101)-C(106)	1.507(11)
C(1)-C(2)	1.559(10)	C(1)-C(6)	1.562(11)
C(2)-C(3)	1.545(11)	C(3)-C(4)	1.525(11)
C(4)-C(5)	1.558(10)	C(5)-C(6)	1.547(10)
C(7)-C(8)	1.378(11)	C(7)-C(12)	1.388(11)
C(8)-C(9)	1.387(11)	C(9)-C(10)	1.387(13)
C(10)-C(11)	1.374(14)	C(10)-C(13)	1.515(13)
C(11)-C(12)	1.373(13)	C(14)-C(15)	1.389(11)
C(14)-C(19)	1.389(11)	C(15)-C(16)	1.371(12)
C(16)-C(17)	1.387(13)	C(17)-C(18)	1.373(13)
C(17)-C(20)	1.504(13)	C(18)-C(19)	1.387(12)
C(21)-C(22)	1.461(16)	C(22)-C(23)	1.527(14)
C(23)-C(24)	1.48(2)	C(25)-C(26)	1.524(12)
C(26)-C(27)	1.504(14)	C(27)-C(28)	1.510(14)
C(29)-C(33)	1.58(2)	C(29)-C(30)	1.67(3)
C(30)-C(31)	1.07(3)	C(31)-C(32)	1.76(3)
C(33)-C(34)	1.52(4)	C(34)-C(35)	1.32(4)
C(101)-C(106)	1.547(11)	C(101)-C(102)	1.575(11)
C(102)-C(103)	1.555(13)	C(103)-C(104)	1.564(11)
C(104)-C(105)	1.547(11)	C(105)-C(106)	1.540(11)
C(107)-C(108)	1.378(12)	C(107)-C(112)	1.392(12)
C(108)-C(109)	1.390(13)	C(109)-C(110)	1.364(16)
C(110)-C(111)	1.377(17)	C(110)-C(113)	1.520(15)
C(111)-C(112)	1.397(15)	C(114)-C(119)	1.380(12)
C(114)-C(115)	1.390(12)	C(115)-C(116)	1.375(12)
C(116)-C(117)	1.390(14)	C(117)-C(118)	1.389(15)
C(117)-C(120)	1.511(13)	C(118)-C(119)	1.382(13)
C(121)-C(122)	1.509(14)	C(122)-C(123)	1.531(15)
C(123)-C(124)	1.515(14)	C(125)-C(126)	1.52(2)
C(126)-C(127)	1.467(16)	C(127)-C(128)	1.52(2)
C(129)-C(130)	1.56(2)	C(129)-C(133)	1.62(4)
C(130)-C(131)	1.51(3)	C(131)-C(132)	1.40(4)
C(133)-C(134)	1.39(4)	C(134)-C(135)	1.46(4)
C(25)-Sn(1)-C(29)	108.8(4)	C(25)-Sn(1)-C(21)	110.0(5)
C(29)-Sn(1)-C(21)	112.0(6)	C(25)-Sn(1)-C(1)	108.5(3)
C(29)-Sn(1)-C(1)	108.1(4)	C(21)-Sn(1)-C(1)	109.4(4)
C(125)-Sn(2)-C(121)	108.6(6)	C(125)-Sn(2)-C(102)	108.1(4)
C(121)-Sn(2)-C(102)	111.4(5)	C(125)-Sn(2)-C(129)	114.3(8)
C(121)-Sn(2)-C(129)	107.5(6)	C(102)-Sn(2)-C(129)	107.0(4)
O(2)-S(1)-O(1)	120.6(4)	O(2)-S(1)-N(1)	105.8(4)
O(1)-S(1)-N(1)	105.1(4)	O(2)-S(1)-C(7)	107.3(4)
O(1)-S(1)-C(7)	108.2(4)	N(1)-S(1)-C(7)	109.6(4)
O(4)-S(2)-O(3)	119.0(4)	O(4)-S(2)-C(14)	109.2(4)
O(3)-S(2)-C(14)	108.5(4)	O(4)-S(2)-C(2)	110.2(4)
O(3)-S(2)-C(2)	105.8(4)	C(14)-S(2)-C(2)	102.9(4)
O(101)-S(101)-O(102)	120.1(4)	O(101)-S(101)-N(101)	105.4(4)
O(102)-S(101)-N(101)	106.1(4)	O(101)-S(101)-C(107)	107.1(4)
O(102)-S(101)-C(107)	107.4(4)	N(101)-S(101)-C(107)	110.8(4)
O(103)-S(102)-O(104)	118.7(4)	O(103)-S(102)-C(114)	108.5(4)
O(104)-S(102)-C(114)	108.3(4)	O(103)-S(102)-C(101)	110.6(4)
O(104)-S(102)-C(101)	106.4(4)	C(114)-S(102)-C(101)	103.2(4)
C(6)-N(1)-C(3)	97.3(6)	C(6)-N(1)-S(1)	125.3(6)
C(3)-N(1)-S(1)	123.6(5)	C(103)-N(101)-C(106)	97.9(6)

C(103)-N(101)-S(101)	125.5(6)	C(106)-N(101)-S(101)	123.5(5)
C(2)-C(1)-C(6)	100.7(6)	C(2)-C(1)-Sn(1)	114.4(5)
C(6)-C(1)-Sn(1)	110.0(5)	C(3)-C(2)-C(1)	105.0(6)
C(3)-C(2)-S(2)	113.1(6)	C(1)-C(2)-S(2)	116.2(6)
N(1)-C(3)-C(4)	103.5(6)	N(1)-C(3)-C(2)	95.6(6)
C(4)-C(3)-C(2)	111.6(7)	C(3)-C(4)-C(5)	103.1(6)
C(6)-C(5)-C(4)	102.8(6)	N(1)-C(6)-C(5)	104.2(6)
N(1)-C(6)-C(1)	98.2(6)	C(5)-C(6)-C(1)	107.8(7)
C(8)-C(7)-C(12)	120.3(8)	C(8)-C(7)-S(1)	119.3(6)
C(12)-C(7)-S(1)	120.3(7)	C(7)-C(8)-C(9)	119.3(8)
C(8)-C(9)-C(10)	120.8(9)	C(11)-C(10)-C(9)	118.5(8)
C(11)-C(10)-C(13)	120.8(10)	C(9)-C(10)-C(13)	120.6(11)
C(12)-C(11)-C(10)	121.7(8)	C(11)-C(12)-C(7)	119.2(9)
C(15)-C(14)-C(19)	119.8(8)	C(15)-C(14)-S(2)	121.2(6)
C(19)-C(14)-S(2)	119.0(7)	C(16)-C(15)-C(14)	119.4(8)
C(15)-C(16)-C(17)	121.6(9)	C(18)-C(17)-C(16)	118.7(8)
C(18)-C(17)-C(20)	119.5(10)	C(16)-C(17)-C(20)	121.8(10)
C(17)-C(18)-C(19)	120.9(8)	C(18)-C(19)-C(14)	119.6(8)
C(22)-C(21)-Sn(1)	114.9(8)	C(21)-C(22)-C(23)	115.5(11)
C(24)-C(23)-C(22)	114.8(13)	C(26)-C(25)-Sn(1)	114.7(6)
C(27)-C(26)-C(25)	113.7(8)	C(26)-C(27)-C(28)	115.2(9)
C(33)-C(29)-C(30)	48.3(11)	C(33)-C(29)-Sn(1)	122.7(10)
C(30)-C(29)-Sn(1)	95.2(11)	C(31)-C(30)-C(29)	139(3)
C(30)-C(31)-C(32)	112(3)	C(34)-C(33)-C(29)	100.7(15)
C(35)-C(34)-C(33)	124(2)	C(106)-C(101)-C(102)	103.7(7)
C(106)-C(101)-S(102)	112.6(6)	C(102)-C(101)-S(102)	118.5(6)
C(103)-C(102)-C(101)	101.9(6)	C(103)-C(102)-Sn(2)	110.4(7)
C(101)-C(102)-Sn(2)	115.0(5)	N(101)-C(103)-C(102)	98.3(6)
N(101)-C(103)-C(104)	102.7(6)	C(102)-C(103)-C(104)	108.0(8)
C(105)-C(104)-C(103)	103.7(6)	C(106)-C(105)-C(104)	102.9(6)
N(101)-C(106)-C(105)	103.4(6)	N(101)-C(106)-C(101)	96.1(6)
C(105)-C(106)-C(101)	111.2(7)	C(108)-C(107)-C(112)	120.9(9)
C(108)-C(107)-S(101)	119.9(7)	C(112)-C(107)-S(101)	119.2(7)
C(107)-C(108)-C(109)	119.3(9)	C(110)-C(109)-C(108)	121.1(11)
C(109)-C(110)-C(111)	119.1(10)	C(109)-C(110)-C(113)	120.9(14)
C(111)-C(110)-C(113)	120.0(13)	C(110)-C(111)-C(112)	121.6(10)
C(107)-C(112)-C(111)	117.9(10)	C(119)-C(114)-C(115)	120.2(8)
C(119)-C(114)-S(102)	120.7(7)	C(115)-C(114)-S(102)	119.1(7)
C(116)-C(115)-C(114)	119.6(9)	C(115)-C(116)-C(117)	121.5(9)
C(116)-C(117)-C(118)	117.6(9)	C(116)-C(117)-C(120)	121.2(10)
C(118)-C(117)-C(120)	121.2(11)	C(119)-C(118)-C(117)	121.8(10)
C(114)-C(119)-C(118)	119.3(9)	C(122)-C(121)-Sn(2)	113.6(8)
C(121)-C(122)-C(123)	113.1(9)	C(124)-C(123)-C(122)	112.2(10)
C(126)-C(125)-Sn(2)	113.9(9)	C(127)-C(126)-C(125)	115.1(14)
C(126)-C(127)-C(128)	112.0(16)	C(130)-C(129)-C(133)	47.1(15)
C(130)-C(129)-Sn(2)	123.5(11)	C(133)-C(129)-Sn(2)	90.0(13)
C(131)-C(130)-C(129)	114.1(17)	C(132)-C(131)-C(130)	114(3)
C(134)-C(133)-C(129)	98(3)	C(133)-C(134)-C(135)	114(3)

Symmetry transformations used to generate equivalent atoms:

Table 4 - Anisotropic displacement parameters ($Å^2 \times 10^3$) for stannane **412**. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

Atom	U11	U22	U33	U23	U13	U12
Sn(1)	42(1)	35(1)	128(1)	-4(1)	30(1)	-1(1)
Sn(2)	48(1)	38(1)	218(1)	-13(1)	34(1)	2(1)
S(1)	38(1)	43(1)	61(1)	-10(1)	8(1)	-4(1)
S(2)	34(1)	51(1)	57(1)	-4(1)	0(1)	-1(1)
S(101)	45(1)	47(1)	75(2)	1(1)	12(1)	-9(1)
S(102)	41(1)	52(1)	74(2)	-13(1)	13(1)	-12(1)
O(1)	36(3)	78(4)	80(5)	-30(4)	13(3)	-5(3)
O(2)	69(4)	39(3)	58(4)	-1(3)	9(3)	-6(3)
O(3)	44(3)	59(4)	67(4)	-9(3)	-7(3)	8(3)

O(4)	39(3)	63(4)	67(4)	5(3)	1(3)	-9(3)
O(101)	105(6)	55(4)	85(5)	24(4)	21(5)	-3(4)
O(102)	42(3)	76(4)	86(5)	-23(4)	20(3)	-14(3)
O(103)	54(4)	71(4)	87(5)	-7(4)	23(4)	-24(3)
O(104)	48(4)	60(4)	70(4)	-16(3)	-5(3)	-1(3)
N(1)	30(3)	39(3)	65(5)	-8(3)	7(3)	1(3)
N(101)	31(3)	42(4)	62(5)	-6(3)	8(3)	-2(3)
C(1)	28(4)	40(4)	62(5)	-6(4)	4(4)	0(3)
C(2)	29(4)	41(4)	68(6)	-5(4)	2(4)	2(3)
C(3)	31(4)	45(4)	65(6)	-16(4)	-5(4)	5(3)
C(4)	46(5)	41(4)	51(5)	-4(4)	-16(4)	2(3)
C(5)	33(4)	44(4)	54(5)	4(4)	-6(4)	-4(3)
C(6)	28(4)	38(4)	63(6)	-3(4)	8(4)	-2(3)
C(7)	46(5)	33(4)	57(5)	-2(4)	4(4)	3(3)
C(8)	47(5)	39(4)	50(5)	5(4)	-2(4)	-1(3)
C(9)	57(5)	59(6)	37(5)	2(4)	-16(4)	-20(4)
C(10)	103(8)	46(5)	36(5)	-2(4)	4(5)	-25(5)
C(11)	104(8)	33(4)	47(6)	3(4)	-4(5)	10(5)
C(12)	57(5)	45(5)	53(5)	-1(4)	-11(4)	15(4)
C(13)	147(12)	58(7)	87(9)	-7(6)	24(8)	-51(7)
C(14)	39(4)	53(5)	50(5)	-6(4)	8(4)	-3(4)
C(15)	40(4)	72(6)	26(4)	-3(4)	4(3)	2(4)
C(16)	67(6)	65(6)	40(5)	-19(4)	-1(4)	6(5)
C(17)	76(6)	64(6)	21(4)	-12(4)	-4(4)	-10(5)
C(18)	53(5)	78(6)	37(5)	3(5)	3(4)	-13(5)
C(19)	39(5)	76(6)	46(5)	-16(5)	7(4)	-4(4)
C(20)	117(10)	83(8)	47(6)	-25(6)	-14(6)	-24(7)
C(21)	57(7)	43(6)	290(20)	-8(9)	69(10)	-10(5)
C(22)	50(6)	122(10)	56(6)	22(6)	-9(5)	-26(6)
C(23)	55(7)	106(10)	171(15)	54(10)	6(8)	-22(7)
C(24)	132(14)	330(30)	59(9)	-56(13)	18(8)	-138(17)
C(25)	52(5)	35(4)	90(8)	-2(4)	10(5)	3(4)
C(26)	51(6)	42(5)	137(11)	-11(6)	26(6)	4(4)
C(27)	65(7)	57(6)	129(11)	-15(6)	33(7)	5(5)
C(28)	73(8)	81(8)	128(11)	-30(8)	34(8)	-5(6)
C(29)	139(12)	50(6)	100(10)	14(6)	48(9)	4(7)
C(30)	120(20)	54(13)	82(17)	-25(12)	-2(15)	30(13)
C(31)	67(14)	55(13)	140(20)	25(14)	0(15)	-6(11)
C(32)	74(16)	77(15)	57(15)	17(11)	1(12)	-25(13)
C(33)	66(12)	41(9)	58(12)	11(8)	-11(10)	-8(8)
C(34)	200(30)	77(16)	49(14)	-14(12)	-54(18)	60(20)
C(35)	55(18)	280(60)	110(30)	-100(30)	3(17)	-50(30)
C(101)	30(4)	48(5)	70(6)	-12(4)	9(4)	-8(3)
C(102)	30(4)	43(5)	116(9)	-12(5)	23(5)	-1(3)
C(103)	32(4)	42(4)	78(7)	-6(4)	11(4)	-2(3)
C(104)	31(4)	52(5)	52(5)	1(4)	-4(4)	-9(3)
C(105)	37(4)	40(4)	73(6)	0(4)	0(4)	-7(3)
C(106)	36(4)	38(4)	69(6)	-8(4)	0(4)	-2(3)
C(107)	42(4)	56(5)	40(5)	4(4)	-8(4)	-10(4)
C(108)	64(6)	50(5)	63(6)	-3(4)	-12(5)	-3(4)
C(109)	108(9)	58(6)	48(6)	2(5)	-4(6)	-19(6)
C(110)	101(10)	94(9)	47(6)	-3(6)	-5(6)	-47(8)
C(111)	55(6)	130(11)	65(7)	5(7)	-12(5)	-34(7)
C(112)	50(5)	95(7)	35(5)	13(5)	-16(4)	-1(5)
C(113)	181(16)	144(14)	90(10)	-21(9)	2(10)	-115(13)
C(114)	48(5)	50(5)	62(6)	-13(4)	23(4)	-14(4)
C(115)	55(5)	61(6)	55(6)	-15(5)	11(4)	-14(4)
C(116)	64(6)	76(7)	51(6)	-16(5)	12(5)	-29(5)
C(117)	98(8)	62(6)	48(6)	-13(5)	22(6)	-26(6)
C(118)	94(8)	67(7)	86(8)	-22(6)	49(7)	-11(6)
C(119)	59(6)	59(6)	97(8)	-22(6)	41(6)	-15(5)
C(120)	131(11)	68(7)	82(9)	-27(6)	8(8)	-30(7)
C(121)	51(6)	57(7)	210(16)	-30(8)	11(8)	7(5)
C(122)	57(6)	48(6)	134(11)	-5(6)	24(7)	-1(5)
C(123)	59(6)	61(6)	113(10)	1(6)	2(6)	2(5)
C(124)	73(8)	92(9)	134(12)	-8(8)	36(8)	-7(7)
C(125)	63(8)	35(6)	440(30)	-21(11)	48(13)	-8(5)
C(126)	59(7)	123(11)	132(12)	52(10)	-14(7)	-24(7)
C(127)	76(9)	137(14)	183(17)	79(13)	-26(10)	-38(9)

C(128)	179(18)	340(30)	79(11)	-47(14)	9(11)	-190(20)
C(129)	96(10)	67(8)	187(16)	36(9)	1(10)	21(7)
C(130)	52(10)	45(10)	54(12)	4(8)	-24(9)	-16(8)
C(131)	78(16)	37(11)	150(30)	13(15)	-2(17)	-22(10)
C(132)	74(17)	130(30)	90(20)	-8(19)	5(15)	-23(16)
C(133)	240(50)	110(30)	57(18)	6(16)	-30(20)	-10(30)
C(134)	310(60)	63(19)	70(20)	10(16)	60(30)	30(30)
C(135)	360(60)	190(40)	43(16)	40(20)	-10(30)	150(40)

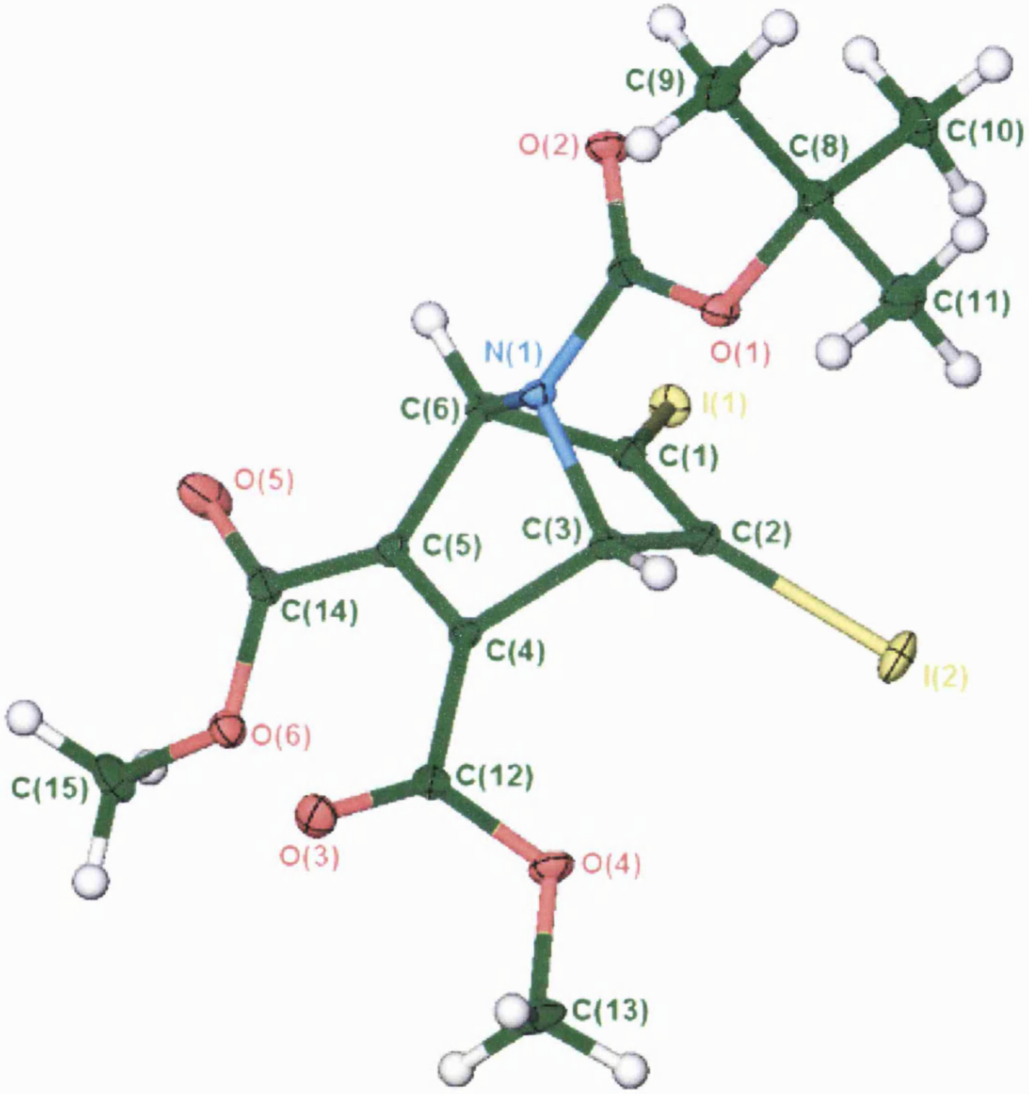
Table 5 - Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for stannae **412**

Atom	x	y	z	U(eq)
H(1)	5403	8263	2019	52
H(2)	3101	8233	2313	55
H(4A)	4358	9627	2731	56
H(4B)	4393	9415	2026	56
H(5A)	6089	9035	2265	53
H(5B)	6101	9283	2953	53
H(8)	6310	9036	4231	55
H(9)	7396	9750	4414	62
H(11)	4563	10580	4186	74
H(12)	3477	9880	3968	62
H(13A)	6282	10984	4463	145
H(13B)	7286	10754	4073	145
H(13C)	7262	10661	4813	145
H(15)	4631	7804	883	55
H(16)	4055	7036	510	69
H(18)	763	7399	697	67
H(19)	1321	8164	1110	65
H(20A)	1656	6448	681	125
H(20B)	2618	6464	174	125
H(20C)	1374	6684	3	125
H(21A)	2868	7206	3209	155
H(21B)	2541	7530	2601	155
H(22A)	3163	6528	2595	92
H(22B)	2908	6848	1975	92
H(23A)	1246	6609	2864	133
H(23B)	981	6948	2262	133
H(24A)	300	6159	2078	260
H(24B)	1552	5936	2215	260
H(24C)	1294	6275	1611	260
H(25A)	5747	6672	2240	71
H(25B)	5098	6956	1672	71
H(26A)	6648	7536	1673	91
H(26B)	7306	7211	2201	91
H(27A)	6713	6869	968	99
H(27B)	7376	6546	1496	99
H(28A)	8661	6845	786	140
H(28B)	8958	7080	1462	140
H(28C)	8294	7401	931	140
H(29A)	6308	7681	3607	114
H(29B)	5172	7513	3922	114
H(30A)	4798	6937	4170	101
H(30B)	4593	6817	3454	101
H(31A)	6326	6481	3759	104
H(31B)	5075	6267	3587	104
H(32A)	5724	5982	4712	104
H(32B)	4587	6306	4752	104
H(32C)	5806	6547	4932	104
H(33A)	6262	6665	3526	66
H(33B)	7145	6989	3961	66
H(34A)	6211	6716	4749	132
H(34B)	5318	7133	4546	132
H(35A)	4490	6485	4831	223
H(35B)	5115	6160	4323	223

H(35C)	4218	6577	4098	223
H(101)	6893	4115	2776	59
H(102)	4572	4050	3045	75
H(10A)	3886	3284	2727	54
H(10B)	3962	3067	2028	54
H(10C)	5581	2928	3001	60
H(10D)	5673	2723	2295	60
H(108)	6503	2527	1068	71
H(109)	5407	1841	758	86
H(111)	2703	2712	373	100
H(112)	3767	3414	681	73
H(11A)	2460	1861	252	208
H(11B)	3359	1502	611	208
H(11C)	3532	1654	-103	208
H(115)	8696	4163	3961	68
H(116)	9212	4918	4400	76
H(118)	5912	5210	4699	97
H(119)	5376	4457	4252	85
H(12A)	8782	5650	4958	140
H(12B)	7560	5694	5257	140
H(12C)	7741	5906	4569	140
H(12D)	4784	5302	3535	127
H(12E)	4366	5680	2995	127
H(12F)	3087	4841	3362	95
H(12G)	2668	5221	2824	95
H(12H)	2998	5478	4126	93
H(12I)	2595	5862	3589	93
H(12J)	1012	5579	4129	148
H(12K)	1289	5023	3931	148
H(12L)	883	5417	3408	148
H(12M)	7379	4833	2579	212
H(12N)	7066	5144	1958	212
H(12O)	6696	5846	2569	127
H(12P)	6961	5536	3196	127
H(12Q)	8605	5754	2315	160
H(12R)	8855	5471	2966	160
H(12S)	9383	6313	3056	300
H(12T)	8397	6188	3524	300
H(12U)	8092	6472	2879	300
H(12V)	4352	4724	1225	140
H(12W)	3296	4953	1602	140
H(13D)	3194	5403	905	62
H(13E)	2999	5557	1615	62
H(13F)	4007	6190	1241	107
H(13G)	4932	5882	1655	107
H(13H)	5642	6114	750	149
H(13I)	4623	5838	365	149
H(13J)	5542	5525	777	149
H(13K)	4328	5747	1767	161
H(13L)	5487	5513	1508	161
H(13M)	4459	5930	731	177
H(13N)	3389	5581	843	177
H(13O)	4323	5328	-20	296
H(13P)	4398	4908	508	296
H(13Q)	5477	5255	402	296

Appendix F

Crystal structure and data for diiodide **423**



5,6-Diiodo-7-aza-bicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylic acid tert-butyl ester dimethyl ester

Table 1 - Crystal data and structure refinement for diiodide **423**

Identification code	diiodide **423**
Empirical formula	C15 H17 I2 N O6
Formula weight	561.10
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 10.8230(1)Å α = 90°
	b = 14.8030(1)Å β = 97.433(1)°
	c = 12.2770(1)Å γ = 90°
Volume	1950.40(3) Å^3
Z	4
Density (calculated)	1.911 Mg/m^3
Absorption coefficient	3.252 mm^{-1}
F(000)	1072
Crystal size	0.25 x 0.20 x 0.20 mm
Theta range for data collection	3.63 to 33.14 .
Index ranges	-16<=h<=16; -22<=k<=22; -18<=l<=18
Reflections collected	45779
Independent reflections	7406 [R(int) = 0.0513]
Reflections observed (>2σ)	5992
Data Completeness	0.997
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.53 and 0.42
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7406 / 0 / 223
Goodness-of-fit on F^2	0.996
Final R indices [I>2σ(I)]	R_1 = 0.0352 wR_2 = 0.0937
R indices (all data)	R_1 = 0.0478 wR_2 = 0.1009
Largest diff. peak and hole	2.622 and -2.124 eÅ^{-3}

Table 2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for diiodide **423**. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

Atom	x	y	z	U(eq)
I(1)	3871(1)	3630(1)	12100(1)	28(1)
I(2)	1190(1)	3552(1)	9530(1)	39(1)
O(1)	3514(2)	1210(1)	8683(2)	25(1)
O(2)	5175(2)	1294(2)	10030(2)	30(1)
O(3)	-325(2)	121(1)	11339(2)	33(1)
O(4)	-723(2)	1456(1)	10499(2)	31(1)
O(5)	3056(2)	1096(2)	13833(2)	52(1)
O(6)	989(2)	996(1)	13368(2)	26(1)
N(1)	3174(2)	1119(1)	10424(2)	20(1)
C(1)	3087(2)	2552(2)	11198(2)	22(1)
C(2)	2186(2)	2521(2)	10342(2)	22(1)
C(3)	1916(2)	1498(2)	10109(2)	20(1)
C(4)	1324(2)	1139(2)	11105(2)	20(1)
C(5)	2219(2)	1190(2)	11969(2)	20(1)
C(6)	3378(2)	1556(2)	11526(2)	20(1)
C(7)	4072(2)	1232(2)	9717(2)	22(1)
C(8)	4227(2)	1203(2)	7738(2)	25(1)
C(9)	5001(3)	349(2)	7767(3)	35(1)
C(10)	5004(3)	2049(2)	7729(3)	38(1)
C(11)	3193(3)	1190(3)	6776(3)	37(1)
C(12)	10(2)	835(2)	11025(2)	23(1)
C(13)	-2046(3)	1251(2)	10333(3)	42(1)
C(14)	2158(2)	1085(2)	13154(2)	25(1)
C(15)	823(3)	978(2)	14515(2)	37(1)

Table 3 - Bond lengths [Å] and angles [°] for diiodide **423**

I(1)-C(1)	2.061(2)	I(2)-C(2)	2.051(2)
O(1)-C(7)	1.334(3)	O(1)-C(8)	1.474(3)
O(2)-C(7)	1.209(3)	O(3)-C(12)	1.198(3)
O(4)-C(12)	1.326(3)	O(4)-C(13)	1.452(3)
O(5)-C(14)	1.195(3)	O(6)-C(14)	1.332(3)
O(6)-C(15)	1.444(3)	N(1)-C(7)	1.394(3)
N(1)-C(3)	1.477(3)	N(1)-C(6)	1.490(3)
C(1)-C(2)	1.338(3)	C(1)-C(6)	1.551(3)
C(2)-C(3)	1.561(3)	C(3)-C(4)	1.546(3)
C(4)-C(5)	1.342(3)	C(4)-C(12)	1.483(3)
C(5)-C(14)	1.474(4)	C(5)-C(6)	1.529(3)
C(8)-C(10)	1.510(4)	C(8)-C(9)	1.513(4)
C(8)-C(11)	1.519(4)		
C(7)-O(1)-C(8)	122.06(19)	C(12)-O(4)-C(13)	116.1(2)
C(14)-O(6)-C(15)	115.8(2)	C(7)-N(1)-C(3)	119.0(2)
C(7)-N(1)-C(6)	118.66(19)	C(3)-N(1)-C(6)	95.51(17)
C(2)-C(1)-C(6)	105.9(2)	C(2)-C(1)-I(1)	131.00(18)
C(6)-C(1)-I(1)	122.73(16)	C(1)-C(2)-C(3)	106.11(19)
C(1)-C(2)-I(2)	129.75(18)	C(3)-C(2)-I(2)	123.94(16)
N(1)-C(3)-C(4)	97.14(18)	N(1)-C(3)-C(2)	100.15(18)
C(4)-C(3)-C(2)	106.03(19)	C(5)-C(4)-C(12)	131.1(2)
C(5)-C(4)-C(3)	106.0(2)	C(12)-C(4)-C(3)	122.9(2)
C(4)-C(5)-C(14)	130.9(2)	C(4)-C(5)-C(6)	106.3(2)
C(14)-C(5)-C(6)	122.1(2)	N(1)-C(6)-C(5)	97.87(18)
N(1)-C(6)-C(1)	100.09(18)	C(5)-C(6)-C(1)	106.30(18)
O(2)-C(7)-O(1)	127.6(2)	O(2)-C(7)-N(1)	123.4(2)
O(1)-C(7)-N(1)	108.9(2)	O(1)-C(8)-C(10)	110.4(2)
O(1)-C(8)-C(9)	109.4(2)	C(10)-C(8)-C(9)	112.7(2)
O(1)-C(8)-C(11)	101.8(2)	C(10)-C(8)-C(11)	111.1(2)
C(9)-C(8)-C(11)	111.0(2)	O(3)-C(12)-O(4)	125.6(2)
O(3)-C(12)-C(4)	125.0(2)	O(4)-C(12)-C(4)	109.3(2)
O(5)-C(14)-O(6)	124.9(3)	O(5)-C(14)-C(5)	123.5(2)
O(6)-C(14)-C(5)	111.7(2)		

Symmetry transformations used to generate equivalent atoms:

Table 4 - Anisotropic displacement parameters ($Å^2 \times 10^3$) for diiodide **423**. The anisotropic displacement factor exponent takes the form: $-2\,gpi^2\,[\,h^2\,a^{*2}\,U11 + ... + 2\,h\,k\,a^*\,b^*\,U$

Atom	U11	U22	U33	U23	U13	U12
I(1)	31(1)	22(1)	30(1)	-5(1)	2(1)	-5(1)
I(2)	46(1)	32(1)	35(1)	8(1)	-5(1)	14(1)
O(1)	20(1)	35(1)	19(1)	-1(1)	1(1)	1(1)
O(2)	18(1)	44(1)	26(1)	-1(1)	0(1)	-1(1)
O(3)	30(1)	30(1)	39(1)	4(1)	-1(1)	-9(1)
O(4)	18(1)	31(1)	43(1)	1(1)	-3(1)	-1(1)
O(5)	30(1)	100(2)	23(1)	8(1)	-4(1)	-19(1)
O(6)	26(1)	31(1)	23(1)	2(1)	5(1)	-1(1)
N(1)	16(1)	24(1)	19(1)	-2(1)	0(1)	1(1)
C(1)	21(1)	21(1)	23(1)	1(1)	3(1)	-2(1)
C(2)	21(1)	20(1)	23(1)	2(1)	2(1)	2(1)
C(3)	17(1)	23(1)	21(1)	-1(1)	1(1)	1(1)
C(4)	19(1)	19(1)	23(1)	0(1)	1(1)	0(1)
C(5)	21(1)	18(1)	22(1)	1(1)	1(1)	0(1)
C(6)	17(1)	20(1)	22(1)	-2(1)	1(1)	1(1)
C(7)	20(1)	22(1)	22(1)	-1(1)	1(1)	0(1)
C(8)	27(1)	28(1)	21(1)	1(1)	4(1)	2(1)
C(9)	40(2)	33(1)	33(1)	-3(1)	7(1)	9(1)
C(10)	43(2)	32(1)	38(2)	6(1)	7(1)	-8(1)
C(11)	35(1)	51(2)	25(1)	0(1)	-2(1)	3(1)
C(12)	20(1)	24(1)	24(1)	-3(1)	2(1)	-3(1)

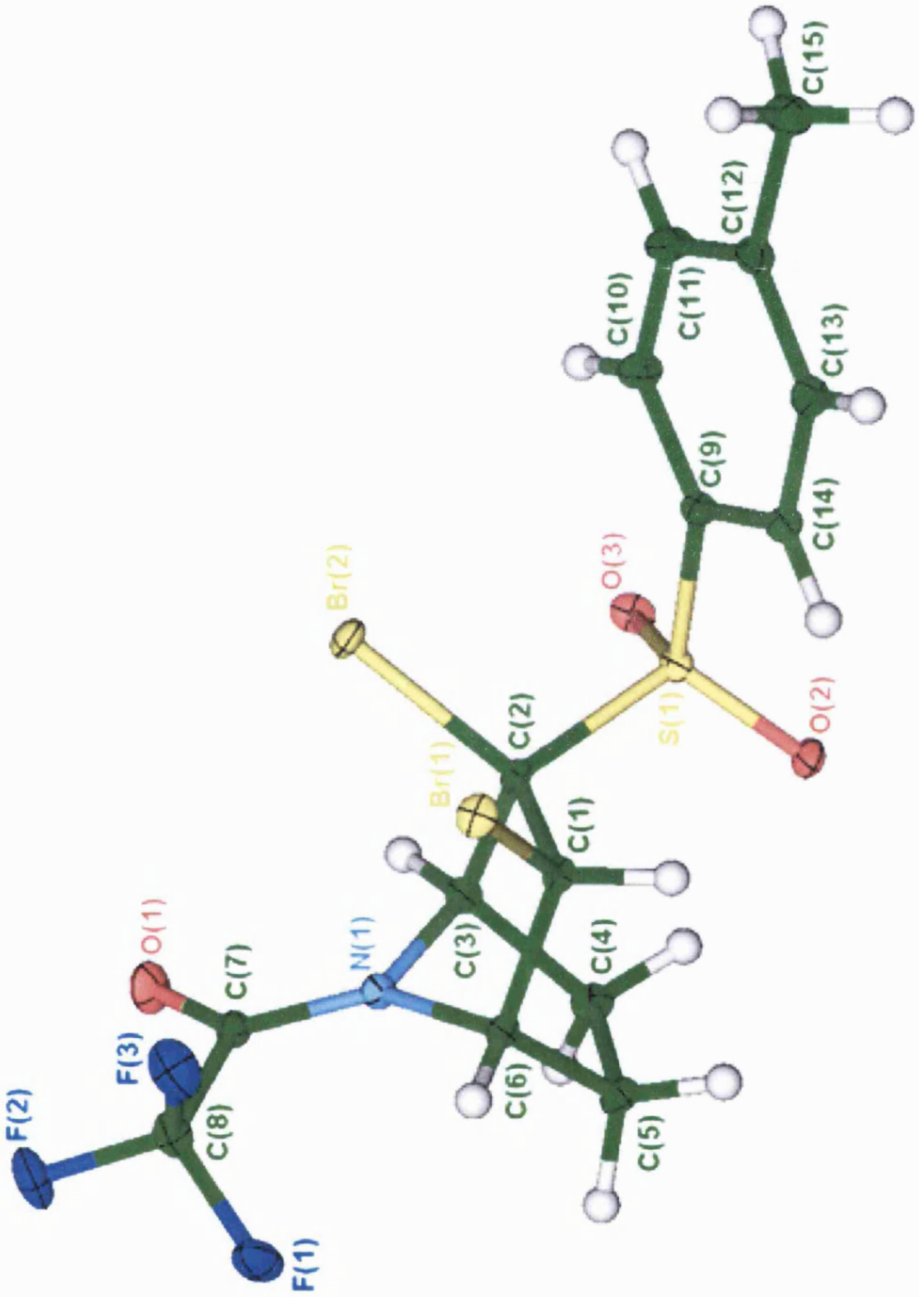
C(13)	18(1)	48(2)	58(2)	-6(2)	-5(1)	0(1)
C(14)	25(1)	26(1)	23(1)	4(1)	2(1)	-4(1)
C(15)	42(2)	47(2)	25(1)	3(1)	12(1)	-9(1)

Table 5 - Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for diiodide **423**

Atom	x	y	z	U(eq)
H(3)	1487	1338	9364	24
H(6)	4197	1437	11981	23
H(9A)	5684	385	8373	53
H(9B)	5344	284	7071	53
H(9C)	4475	-174	7876	53
H(10A)	4483	2579	7819	56
H(10B)	5344	2092	7029	56
H(10C)	5690	2026	8334	56
H(11A)	2661	661	6835	56
H(11B)	3558	1159	6087	56
H(11C)	2692	1741	6785	56
H(13A)	-2190	707	9878	63
H(13B)	-2503	1759	9962	63
H(13C)	-2338	1147	11045	63
H(15A)	1332	493	14886	56
H(15B)	-57	870	14585	56
H(15C)	1082	1559	14854	56

Appendix G

The Crystal structure and data of dibromide **429**



1-[2,3-Dibromo-2-(toluene-4-sulphonyl)-7-aza-bicyclo[2.2.1]hept-7-yl]-2,2,2-trifluoro-ethanone

Table 1 - Crystal data and structure refinement for dibromide **429**

Identification code	dibromide **429**
Empirical formula	C15 H14 Br2 F3 N O3 S
Formula weight	505.15
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.81100(10)Å α = 90°
	b = 13.23200(10)Å β = 101.62°
	c = 12.84800(10)Å γ = 90°
Volume	1800.22(3) $Å^3$
Z	4
Density (calculated)	1.864 Mg/m^3
Absorption coefficient	4.663 mm^{-1}
F(000)	992
Crystal size	0.40 x 0.30 x 0.30 mm
Theta range for data collection	3.48 to 30.05°
Index ranges	-15<=h<=15; -18<=k<=18; -18<=l<=18
Reflections collected	33104
Independent reflections	5249 [R(int) = 0.0631]
Reflections observed (>2σ)	4562
Data Completeness	0.997
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.47 and 0.31
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5249 / 0 / 228
Goodness-of-fit on F^2	1.037
Final R indices [I>2σ(I)]	R_1 = 0.0268 wR_2 = 0.0654
R indices (all data)	R_1 = 0.0338 wR_2 = 0.0686
Largest diff. peak and hole	0.519 and -0.552 $eÅ^{-3}$

Table 2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for dibromide **429**. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor.

Atom	x	y	z	U(eq)
Br(1)	-771(1)	9213(1)	1983(1)	26(1)
Br(2)	554(1)	8646(1)	-72(1)	26(1)
S(1)	1637(1)	6897(1)	1363(1)	20(1)
F(1)	-4537(1)	7711(1)	-114(1)	41(1)
F(2)	-4644(1)	8542(1)	-1568(1)	48(1)
F(3)	-3576(1)	9134(1)	-94(1)	45(1)
O(1)	-2535(2)	7668(1)	-1774(1)	38(1)
O(2)	1368(1)	6248(1)	2192(1)	27(1)
O(3)	2089(1)	6463(1)	482(1)	27(1)
N(1)	-1935(1)	7381(1)	-6(1)	20(1)
C(1)	-653(2)	7797(1)	1630(1)	18(1)
C(2)	152(2)	7526(1)	782(1)	18(1)
C(3)	-761(2)	6818(1)	14(1)	20(1)
C(4)	-1058(2)	5826(1)	550(2)	25(1)
C(5)	-1878(2)	6194(1)	1337(2)	25(1)
C(6)	-1958(2)	7341(1)	1140(1)	19(1)
C(7)	-2700(2)	7740(1)	-871(1)	23(1)
C(8)	-3879(2)	8294(2)	-664(2)	31(1)
C(9)	2706(2)	7825(1)	1967(1)	21(1)
C(10)	3596(2)	8193(2)	1427(2)	28(1)
C(11)	4505(2)	8865(2)	1944(2)	31(1)
C(12)	4516(2)	9172(2)	2982(2)	27(1)
C(13)	3595(2)	8805(2)	3497(2)	26(1)
C(14)	2687(2)	8126(1)	3004(1)	23(1)
C(15)	5529(2)	9883(2)	3539(2)	38(1)

Table 3 - Bond lengths [Å] and angles [°] for dibromide **429**

Br(1)-C(1)	1.9380(16)	Br(2)-C(2)	1.9449(16)
S(1)-O(3)	1.4395(14)	S(1)-O(2)	1.4432(14)
S(1)-C(9)	1.7560(17)	S(1)-C(2)	1.8283(17)
F(1)-C(8)	1.343(3)	F(2)-C(8)	1.324(2)
F(3)-C(8)	1.335(3)	O(1)-C(7)	1.212(2)
N(1)-C(7)	1.332(2)	N(1)-C(3)	1.468(2)
N(1)-C(6)	1.479(2)	C(1)-C(6)	1.547(2)
C(1)-C(2)	1.567(2)	C(2)-C(3)	1.560(2)
C(3)-C(4)	1.546(3)	C(4)-C(5)	1.550(3)
C(5)-C(6)	1.538(2)	C(7)-C(8)	1.539(3)
C(9)-C(10)	1.383(3)	C(9)-C(14)	1.394(2)
C(10)-C(11)	1.390(3)	C(11)-C(12)	1.393(3)
C(12)-C(13)	1.389(3)	C(12)-C(15)	1.510(3)
C(13)-C(14)	1.387(3)		
O(3)-S(1)-O(2)	119.56(9)	O(3)-S(1)-C(9)	109.18(8)
O(2)-S(1)-C(9)	107.62(8)	O(3)-S(1)-C(2)	105.64(8)
O(2)-S(1)-C(2)	106.38(8)	C(9)-S(1)-C(2)	107.93(8)
C(7)-N(1)-C(3)	125.83(15)	C(7)-N(1)-C(6)	135.37(15)
C(3)-N(1)-C(6)	98.73(13)	C(6)-C(1)-C(2)	102.49(13)
C(6)-C(1)-Br(1)	112.07(11)	C(2)-C(1)-Br(1)	117.13(11)
C(3)-C(2)-C(1)	101.99(13)	C(3)-C(2)-S(1)	112.11(11)
C(1)-C(2)-S(1)	112.65(11)	C(3)-C(2)-Br(2)	106.62(11)
C(1)-C(2)-Br(2)	115.88(11)	S(1)-C(2)-Br(2)	107.44(8)
N(1)-C(3)-C(4)	100.53(14)	N(1)-C(3)-C(2)	98.08(13)
C(4)-C(3)-C(2)	112.95(14)	C(3)-C(4)-C(5)	102.77(14)
C(6)-C(5)-C(4)	102.91(14)	N(1)-C(6)-C(5)	100.84(13)
N(1)-C(6)-C(1)	101.22(13)	C(5)-C(6)-C(1)	107.58(14)
O(1)-C(7)-N(1)	125.70(18)	O(1)-C(7)-C(8)	119.35(17)
N(1)-C(7)-C(8)	114.95(15)	F(2)-C(8)-F(3)	108.40(18)
F(2)-C(8)-F(1)	107.48(18)	F(3)-C(8)-F(1)	106.71(17)
F(2)-C(8)-C(7)	110.98(16)	F(3)-C(8)-C(7)	111.80(17)
F(1)-C(8)-C(7)	111.26(17)	C(10)-C(9)-C(14)	121.61(16)
C(10)-C(9)-S(1)	119.15(14)	C(14)-C(9)-S(1)	119.11(14)
C(9)-C(10)-C(11)	118.81(18)	C(10)-C(11)-C(12)	120.83(19)
C(13)-C(12)-C(11)	119.05(18)	C(13)-C(12)-C(15)	120.90(18)
C(11)-C(12)-C(15)	120.05(19)	C(14)-C(13)-C(12)	121.24(17)
C(13)-C(14)-C(9)	118.44(17)		

Symmetry transformations used to generate equivalent atoms:

Table 4 - Anisotropic displacement parameters ($Å^2 \times 10^3$) for dibromide **429**. The anisotropic displacement factor exponent takes the form: $-2\,gpi^2\,[\,h^2\,a^{*2}\,U11 + ... + 2\,h\,k\,a^*\,b^*\,U$

Atom	U11	U22	U33	U23	U13	U12
Br(1)	37(1)	16(1)	27(1)	-7(1)	8(1)	1(1)
Br(2)	31(1)	22(1)	27(1)	8(1)	11(1)	1(1)
S(1)	21(1)	14(1)	24(1)	-2(1)	4(1)	0(1)
F(1)	26(1)	61(1)	37(1)	-1(1)	11(1)	1(1)
F(2)	41(1)	65(1)	33(1)	4(1)	-6(1)	21(1)
F(3)	48(1)	37(1)	48(1)	-12(1)	2(1)	14(1)
O(1)	42(1)	57(1)	16(1)	2(1)	8(1)	9(1)
O(2)	31(1)	18(1)	31(1)	7(1)	2(1)	-1(1)
O(3)	27(1)	23(1)	32(1)	-10(1)	7(1)	1(1)
N(1)	23(1)	25(1)	14(1)	-3(1)	6(1)	2(1)
C(1)	25(1)	13(1)	18(1)	-2(1)	6(1)	1(1)
C(2)	23(1)	13(1)	18(1)	1(1)	6(1)	-1(1)
C(3)	24(1)	22(1)	17(1)	-6(1)	7(1)	2(1)
C(4)	29(1)	17(1)	29(1)	-7(1)	6(1)	-4(1)
C(5)	30(1)	20(1)	25(1)	-1(1)	8(1)	-4(1)
C(6)	24(1)	20(1)	15(1)	-1(1)	7(1)	0(1)
C(7)	26(1)	26(1)	18(1)	0(1)	4(1)	-1(1)
C(8)	30(1)	37(1)	25(1)	-2(1)	1(1)	6(1)

C(9)	21(1)	18(1)	23(1)	-3(1)	3(1)	-1(1)
C(10)	28(1)	31(1)	26(1)	-6(1)	9(1)	-5(1)
C(11)	28(1)	35(1)	31(1)	-4(1)	10(1)	-10(1)
C(12)	27(1)	26(1)	27(1)	-2(1)	0(1)	-3(1)
C(13)	30(1)	27(1)	21(1)	-3(1)	3(1)	-2(1)
C(14)	25(1)	24(1)	22(1)	0(1)	7(1)	-1(1)
C(15)	36(1)	40(1)	35(1)	-6(1)	1(1)	-14(1)

Table 5 - Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for dibromide **429**

Atom	x	y	z	U(eq)
H(1)	-301	7420	2298	22
H(3)	-538	6725	-699	24
H(4A)	-275	5494	930	30
H(4B)	-1532	5348	23	30
H(5A)	-2726	5880	1178	29
H(5B)	-1468	6040	2080	29
H(6)	-2695	7683	1348	23
H(10)	3587	7989	717	33
H(11)	5126	9118	1583	37
H(13)	3588	9023	4200	31
H(14)	2066	7871	3363	28
H(15A)	5173	10562	3562	57
H(15B)	6222	9904	3152	57
H(15C)	5849	9644	4266	57